pp. 939-1048] November, 1948

TROPICAL DISEASES BULLETIN

VOL. 45] 1948 [No. 11

MAIN CONTENTS:

	PAGES
Summary of Recent Abstracts. IX. Leprosy	939–944
Rabies	945–947
Malaria	948–980
Blackwater Fever	980–981
Trypanosomiasis	982–984
Leishmaniasis	984–985
Fevers of the Typhus Group	985–992
Yellow Fever	992–993
Dengue and Allied Fevers...	993–994
Plague	994–998
Cholera	998–1000
Amoebiasis and Intestinal Protozoal Infections ...	1001–1007
Leprosy	1007–1014
Helminthiasis	1015–1023
Deficiency Diseases ...	1023–1026
Sprue	1026–1027
Venoms and Antivenenes...	1027–1030
Dermatology and Fungus Diseases	1030–1031
Tropical Ulcer	1032–1034
Miscellaneous Diseases ...	1034–1035
Protozoology: General ...	1035–1036
Entomology and Insecticides: General	1036–1039
Reports, Surveys and Miscellaneous Papers ...	1039–1043
Book Reviews	1043–1048

For detailed Contents see pp. ii, iv, vi, viii and x

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BUREAU OF HYGIENE AND TROPICAL DISEASES

TROPICAL DISEASES BULLETIN

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SUMMARY OF RECENT ABSTRACTS*

IX. LEPROSY

Epidemiology: Transmission

In the *British Medical Journal* (p. 719) is an account of 6 cases of leprosy which occurred in Britain in persons returned from the Far East. The importance of bearing leprosy in mind in cases of resistant skin lesions is emphasized.

In a survey of 42,811 school children in British Guiana WHARTON (p. 720) found 94 cases of leprosy, 91 of which were early nerve cases. FLOCH and DE LAJUDIE (p. 322) estimate that the incidence of leprosy in French Guiana is about 65 per 1,000, with the highest rates at the age of 6–10 years. Family infections and school infections are common. The same authors (p. 589) give a detailed account of the progress of a considerable number of leprosy patients in French Guiana. They record incubation periods as short as 9 and 15 months in two infants. The proportion of leprosy patients showing lepromatous or mixed lesions is higher in Europeans, Arabs and the penal classes than in the Creole population.

In Cuba a census revealed 2,166 persons suffering from leprosy in 1946. OTEIZA SETIEN *et al.* (pp. 95, 589) show that the incidence of ambulatory cases varied from 0·163 to 0·6 per 1,000 in different parts of the country, and that the rate in intimate contacts was 33·4 per 1,000. There are 2 special hospitals. Infants born in hospital to diseased parents are separated from them at birth, to be brought up away from infection. IBARRA PÉREZ and GONZÁLEZ PRENDES (p. 430) show that the incidence of leprosy in Cuba is in the ratio of 1·52 males to 1 female. In Argentina, FEDERICO GUILLOT and OSVALDO CURCI (p. 591) found the proportion of 1·82 male to 1 female leprosy patient, and the predominance of males is generally noted in other countries. They discuss leprosy in women and its relation to pregnancy.

DHARMENDRA and SEN (p. 324) give an account of familial and contact spread of leprosy in relation to a family in Calcutta.

MOISER (pp. 321, 725) is unable to accept the view that long-continued close contact is necessary for the transmission of leprosy, and puts forward once more his opinion that cockroaches are important in transmission. MUÑOZ RIVAS (p. 1071) again discusses the possibility that leprosy may be transmitted by fleas. He shows that acid-fast organisms are often present in fleas and their

*The information from which this series of summaries has been compiled is given in the abstracts which have appeared in the *Tropical Diseases Bulletin*, 1947, v. 44. References to the abstracts are given under the names of the authors quoted, and the pages on which the abstracts are printed.

larvae in the dwellings of leprosy patients, but not (in his experience) in the dwellings of healthy people. Inoculation of triturated fleas which had fed on leprous patients into monkeys did not give clear-cut evidence. FLOCH and DE LAJUDIE (p. 724) have cultivated acid-fast bacteria from triatomid bugs which had fed on lepromatous tissue, and from mosquitoes caught in leprosy wards. They do not claim that these were leprosy bacilli.

Aetiology

COCHRANE, MENON and PANDIT (p. 322) have repeatedly injected splenectomized monkeys with material from human leprosy patients. Some of the animals were also fed on *Colocasia antiquorum* (which has been thought to predispose to the disease in man), and some were given preliminary injections of Indian ink. Although no dissemination was observed, all the animals except those which received the Indian ink tended to develop strongly positive lepromin reactions after the third injection. COCHRANE and RAMANUJAIN (p. 323) sum up the results of attempts to infect 38 monkeys with human leprosy material, which were made in the course of 6 years' work. They conclude that a positive lepromin reaction can be obtained only after a primary focus has been established and that *Myco. leprae* cannot parasitize the reticulo-endothelial system unless it multiplies in the corium of the skin, and can only develop if the R-E system is intact. In tuberculoid leprosy the formation of epithelioid foci anchors the bacilli and prevents their dissemination throughout the R-E system. But the authors have not been able to provoke disseminated leprosy in the monkeys.

HANKS (p. 323) gives the results of attempts to cultivate leprosy bacilli in small cubes of leprous tissue placed in various fluid culture media or on solid media. He used a careful method to assess any increase in the number of bacilli, but there was no evidence of multiplication in any experiment. He (p. 721) has carried out tissue-culture experiments with lepromatous tissue, and although there was growth of fibroblasts, other cells (containing the bacilli) died and there was no evidence of any growth of the bacilli themselves. The same author (p. 722) continued this kind of work, but with tissue from macular and tuberculoid lesions. The advancing border of the tuberculoid tissue in culture created a stronger impression of viable leprosy bacilli than any other form of leprosy, but this was not maintained as the tissue cells proliferated. Fibroblasts from these resistant forms of leprosy rapidly ingested and destroyed bacilli with which they had been infected.

HANKS (p. 722) continued this work by injecting carbon particles into the explanted tissue before culture. He observed that the fate of the bacilli was similar to that of the accompanying carbon particles, except that the bacilli were less durable. By doubling the carbon dioxide pressure, or by increasing the rate of growth of fibroblasts, the rate of disappearance of the bacilli was increased, and the distribution of leprous lesions in the body is probably influenced by the same conditions as those which affect the fate of bacilli in cultivated fibroblasts. Internal organs have more cells, greater incidence of mitotic cells, more active metabolism and lower *p*H than cells of the peripheral tissues. In work on rat leprosy he (p. 723) has shown that the injection of carbon particles does not influence the dispersal of leprosy bacilli, and is a good control in experiments on multiplication of organisms. HANKS (p. 723) thinks that the turbidity of plasma surrounding tissue cultures of lepromatous material is not due to increase of the numbers of leprosy bacilli, as some investigators have thought, but to calcification of the plasma. There is no evidence of multiplication of the bacilli.

The same author (p. 724) infected chick embryos and chick tissue cultures with bacilli from lepromatous nodules, but there was no sign of proliferation of the bacilli in any of the experiments.

Diagnosis: Tests

DE SOUZA-ARAUJO (p. 1072) describes his method of clamping skin until it is ischaemic, and then puncturing it to obtain lymph for staining in the search for leprosy bacilli. A method for staining leprosy bacilli with Nachtblau (as for tubercle bacilli) is described by HALLBERG (p. 591). It is particularly useful for sections. A method for staining the rounded thickenings sometimes seen in leprosy bacilli is described by DE OLIVEIRA CASTRO (p. 1072); it is based on the Cooper modification of the Ziehl-Neelsen method. FITE *et al.* (p. 1008) describe a satisfactory method of staining leprosy bacilli in paraffin sections; details are given in the original abstract. BURDON (p. 721) has shown, by using the stain Sudan black B for staining lipid material, that true leprosy bacilli do not contain intracellular material which is stained in this way, but that tubercle bacilli, and acid-fast organisms which have been cultivated from leprosy material, do. This supports the view that these cultivated organisms are not true leprosy bacilli, but are saprophytic.

As a result of a large number of examinations made of recruits in India, MCDONALD (p. 592) shows that examination of sections of suspected skin lesions can be very helpful in diagnosis. In 80 positive specimens only 1 was lepromatous; the rest were tuberculoid, with only scanty bacilli, but with the typical lesions and epithelioid-cell and round-cell infiltrations, and a few giant cells. Differentiation from skin tuberculosis is not easy and requires expert interpretation of the sections and of the clinical condition; there is no caseation in the leprosy sections and there may be peripheral neuritis with round-cell reaction.

Three types of lepromin are used by IGNACIO CHALA and LLERAS RESTREPO (p. 823): whole lepromin (which gives a late reaction in tuberculoid leprosy, and sometimes an early reaction); filtered lepromin; and bacillary lepromin. The last is the most active and is recommended for routine work; strongly positive early reactions are given with filtered and bacillary lepromin in tuberculoid leprosy but not in simple macular or anaesthetic nerve leprosy. The preparation of these lepromins is described.

TISSEUIL (p. 325) thinks that the lepromin reaction in tuberculoid leprosy, though positive in both diseased and healthy skin, is not specific, because reactions are also produced by injection of other acid-fast bacilli, and because lepromin sometimes gives positive results in healthy persons. The negative reaction in lepromatous disease is due to the fact that all the tissues, even those apparently healthy, contain the bacilli, and this negative result is specific because other acid-fast organisms give positive results.

GARCIA MIRANDA (p. 431) states that in non-leprous persons, infection with *Myco. tuberculosis* often provokes sensitivity to lepromin as well as to tuberculin. In leprosy patients, however, reactions to these two substances give discordant results. The lepromin test is a gauge of the body's defensive mechanism, and a negative result indicates absence of resistance [see TISSEUIL above]. GINÉS and POLETTI (p. 528) similarly state that positive reactors to tuberculin are also positive to lepromin [see also this *Bulletin*, 1943, v. 40, 247], and they show that inoculation of BCG may induce a state of reactivity to lepromin, and, perhaps, of resistance to leprosy.

CARBONELL and CONTRERAS DUEÑAS (p. 592) compare the histamine skin test, in leprosy, with a test in which a substance (Priscol) is used which acts on the small arteries and arterioles rather than on the capillaries.

Clinical Findings

The classification of leprosy is discussed by MUIR (p. 1073) who recognizes the two characteristic forms, lepromatous and tuberculoid, and the uncharacteristic form which may remain so or which may progress to one of the others, or be a stage in transition of one of the characteristic forms to the

other, or a stage on the way to recovery. Secondary classifications deal with clinical and topographical features, bacteriological findings and the lepromin test.

DAVEY (p. 325) holds that in macular leprosy there is a wide range of lesions which shade into each other, from the mildest of localized tuberculoid lesions to innumerable poorly-defined macules of lepromatous type, without effective localization. The lepromin test is positive in the mild forms and shades to negative in the severe forms. There seems to be an allergic mechanism in all macular forms, which may appear suddenly.

COCHRANE (p. 1073) thinks that the corium of the skin is the site of active development of leprosy bacilli, and is the area of strategic importance in leprosy. The bacilli in the reticulo-endothelial system are mainly saprophytic. In India many cases of child leprosy are benign and non-progressive, and practical consideration need only be given to simple neural leprosy and pre-lepromatous lesions, the latter comprising 5–10 per cent. of all child cases and developing in families in which there is the closest contact with infective patients. The benign cases in children do not require prolonged treatment.

ERMAKOVA (p. 726) shows that there may be injury to the nerves at the root of the tongue in lepromatous leprosy, but that only the sensory nerves are involved.

PARDO-CASTELLO *et al.* (p. 1074) state that nerve involvement occurs in lepromatous and tuberculoid leprosy, but differs in type in that in the former there is cellular infiltration with masses of bacilli, and in the latter there are thick infiltrations of lymphocytes, epithelioid cells and giant cells, but few bacilli, and caseation sometimes occurs. They therefore think that the so-called neural leprosy belongs to the tuberculoid type. This view is not accepted by some workers.

TISSEUIL (p. 726) describes the essential characters of tuberculoid leprosy, which should not be classified under nerve leprosy.

IGNACIO CHALA (p. 430) has described in detail the skin lesions of tuberculoid leprosy. The account of this work cannot well be abstracted further and the description of the various forms seen should be sought in the original. He makes the point that the lepromin test is positive, and that tuberculoid leprosy is not infective and is therefore not a menace to the public health.

DHARMENDRA and SANTRA (p. 324) have studied the course of leprosy in 248 cases observed for 10 years in India. About one-quarter were lepromatous. Definite improvement or complete subsidence occurred in over 40 per cent. of the cases of nerve leprosy.

RADNA (p. 324) describes the progress of a number of untreated cases of early nerve leprosy. Most remained unchanged during several years, but a few improved and more deteriorated. Treatment with Caloncoba and sodium gynocardate was useful in a group of patients with similar lesions.

BIMBAD (p. 214) has investigated the blood glutathione in leprosy, as an aid to the determination of the state of the oxidation-reduction processes in the patient, and hence of the extent of compensation of the leprosy process.

A description of the eye diseases seen in leprosy is given by MAFFRAND (p. 213).

Alopecia is not a rare complication of leprosy ; it occurred in 2·86 per cent. of cases in the United States (FAGET, p. 593).

MOM (p. 1074) points out that the lepra reaction is an allergic phenomenon, and therefore presumably is due to a substance allied to histamine. He has tried benadryl, a synthetic anti-histamine substance, with considerable success, in the treatment of these reactions. POGGE and ROSS (p. 593) have observed evanescent red nodules resembling those of erythema nodosum, in the course of lepra reactions. These are most frequent in lepromatous leprosy. In a

number of cases a definite increase was found in the fasting blood sugar level, and there was evidence of increase of bile pigments in the urine during the reactions. The hyperglycaemia is probably related to the metabolic function of the liver. Treatment of cases of lepra reaction with insulin produced clinical improvement.

Treatment

MUIR (p. 824) discusses the treatment of leprosy with the sulphone preparations, quoting his own previously published work and that of the Carville team. The drugs cost £6 per patient per annum [but at Carville the saving in dressings more than compensates for the cost of the drugs, see p. 594].

FAGET and his colleagues at Carville (p. 594) have issued a report summing up their experience of promin treatment in 177 cases for periods of 1–5 years. The usual course is now to give the drug intravenously 6 days each week for 2 weeks, followed by a rest of 1 week; this cycle is repeated, to give about 207 injections each year. It was necessary to stop treatment in less than 5 per cent. because of untoward reactions. This treatment results in improvement in all major chronic manifestations, with bacteriological and histological improvement. MOM (p. 594) gives the same doses of promin as are the rule at Carville (2 to 5 gm. intravenously each day) but does not allow the same rest periods. His results have been good and have varied with the dosage and length of treatment. He also gives intravenous injections of ascorbic acid each day. He thinks that the use of chaulmoogra as well as promin is an advantage. PEYRI (p. 1075) discusses the incidence of leprosy in a province of Mexico. He has treated 30 patients (16 lepromatous, 4 tuberculoid, 10 uncharacteristic) with promin, 2 gm. intravenously each day for 6 days each week, with an interval of 15 days every two months. Improvement was seen in all after 200–300 gm. had been given. WHARTON (p. 326) observed considerable improvement in 7 lepromatous cases treated with intravenous promin.

MUIR (p. 327) in England gives diasone by the mouth in a dose of 2·0 gm. on each of 3 days each week for 3 weeks, with an interval of 1 week before the course is resumed. This is repeated time after time, and the dose may be pushed to 12 gm. a week for 3 weeks each month if there are no reactions. Slight anaemia is treated with iron, liver and yeast. In this way he obtained favourable results in lepromatous leprosy, which had not been possible with chaulmoogra alone. FERNANDEZ and CARBONI (p. 595) have had considerable success with diasone given by mouth in tablets containing one-third of a gramme each. The daily dose best tolerated is 2 gm. for 8 weeks, followed by a rest of 3–4 weeks, and repeated. Intolerance may be noted after 2 weeks, but usually disappears if the drug is temporarily stopped, and there may be methaemoglobinaemia and anaemia which usually responds to anti-anaemia treatment. In lepromatous leprosy there is often marked improvement, with softening of the nodules and reduction in size.

FAGET, POGGE and JOHANSEN (p. 326) record some considerable benefit in 7 patients with advanced lepromata treated for 1 year with promizole. The same authors (p. 326) show that in 104 patients treated with diasone by mouth, and observed up to 2½ years, about one-quarter became bacteriologically negative and two-thirds showed improvement. It was necessary to discontinue treatment in a quarter of the patients, for various reasons, but in the rest the drug was well tolerated. The daily dose was gradually increased from 0·33 gm. to 1·0 gm. for adults.

FAGET (p. 727) sums up his experiences with promin, diasone and promizole, the results of which have been very similar. The active principle of them all is apparently the diamino-diphenyl sulphone. Improvement was noted in almost all cases within 3 years, often in a much shorter period.

In an account of the work done under most difficult conditions at the large leprosy hospital in Malaya during the years of Japanese occupation, RYRIE (p. 720) remarks that the lack of Hydnocarpus oil convinced him of its value. BEAUDIMENT *et al.* (p. 727) discuss the methods of treatment (largely with neutralized chaulmoogra oils) and prevention (agricultural colonies for infective patients) used in the French colonies. BARMAN (p. 908) notes that chaulmoogra oil irritates the stomach, but he has given it in dogs and in man by duodenal tube, and has satisfied himself that it is effectively absorbed.

Penicillin is apparently useless in leprosy (FIGUEREDO and DESAI; PANJA, p. 214).

REENSTIERNA (p. 728) states that electrophoretic analysis of his anti-leprosy serum shows that it contains more gamma globulin than normal serum, and this he thinks is due to the presence of antibodies. The serum was prepared against an acid-fast bacillus cultivated from a patient with leprosy, and regarded by the author as the cause of the disease [though many other leprologists would probably not accept it].

Improvement was observed in a number of cases of nerve leprosy treated by FIGUEREDO and DESAI (p. 214) with intravenous methylene blue.

Good results in the treatment of leprous ulcers were achieved by LANGUILLON (p. 596) who used Tisseuil's method of intramuscular injections of acetylcholine hydrochloride.

MOM and BERNAL (p. 596) have used a weak solution of tyrothricin as a spray for leprous ulcers, with great success; 14 of 15 healed though they had resisted other treatments.

Control

MACKAY (p. 720) shows that at the Makete leprosy settlement in Tanganyika Territory there are about 1,500 inmates. Each patient has not less than 5 acres of land and can therefore become self-supporting. Admission is voluntary and there is rarely need to separate husbands and wives, because conjugal infection is rare. The incidence of leprosy in the children is also surprisingly low. In Central Africa only 5–10 per cent. of cases are lepromatous.

AUSTIN (p. 728) defends the system of compulsory segregation of leprosy patients in the scattered islands of Fiji, where a voluntary system would not enable earlier cases to be found and treated. ROGERS agrees that it is evidently a procedure suitable to those conditions, but condemns, for Asia and Africa, where the bulk of cases occur, the indiscriminate compulsory isolation of all types of leprosy, including the large numbers of non-infective nerve cases.

The problem of home isolation of leprosy patients in the Philippines is discussed in the *International Journal of Leprosy* (p. 327). Under the existing law, only bacteriologically positive patients are isolated in institutions; negative patients are placed on parole. In the opinion of some of the members of the staff of the public health department, home isolation is likely to fail, and it would be unwise to relax the regulations in so highly endemic an area as the Philippines.

FAGET (p. 588) contributes a history of the National Leprosarium, Carville, U.S.A., where much work on treatment with promin and diasone has recently been done. In 51 years only one attendant has developed the disease.

CHALA (p. 597) describes the leprosy institutions of Colombia, where there are 3 large leprosaria and 11 dispensaries. *Charles Wilcocks*

RABIES

REMLINGER, P. & BAILLY, J. La rage et le traitement antirabique pendant ces vingt dernières années. [**Rabies and Anti-Rabies Treatment during the Last Twenty Years.**] *Biol. Méd.* 1948, June–July–Aug., v. 37, Nos. 6–7–8, 101–28. [247 refs.]

In this exceedingly informative article the authors review the most important work published on rabies and on its specific treatment during the past 20 years.

The following paragraphs summarize the points on which emphasis is laid:

The causal agent of rabies is a virulent substance of a protein nature. Endowed with powers of assimilation, it is capable of cultivation, particularly on the chorio-allantoic membrane of the chick embryo.

The Viverridae (civet family) in South Africa; Desmodidae (vampire bats) in Paraguay, Argentine and British West Indies; and skunks in the United States have to be added to the list of animals that transmit the infection in nature.

In West Africa, Equatorial Africa and in tropical countries generally, rabies and rabies virus behave exactly as in temperate regions.

The rabies virus occurs not only in the nervous system and salivary glands but also, owing to its central and peripheral nervous distribution, in almost every organ. It has been demonstrated in the suprarenals, spleen, liver, kidney, lung, testicle, Harder's gland, retina, choroid, vitreous body and crystalline lens, but not in the aqueous humour.

The Swiss mouse (preferably) and the white mouse are, in the opinion of many, animals of choice for experimental work on rabies. The former, ten times more susceptible to rabies virus than the rabbit or guineapig, is incomparable for assessment of the immunizing power of different anti-rabies vaccines (WEBSTER).

The "singleness" of street virus contrasts with the "plurality" of fixed virus—a virus "fixed" only in name. Fixed viruses differ among themselves more than street viruses; on repeated "passage" the former become more and more sensitive to the action of desiccation and of glycerin, less and less to that of dilution and of ether. Anti-rabies institutes should have subjected to periodic control the strains of fixed virus used in the preparation of their vaccines. Desiccation does not attenuate; it preserves the rabies virus. Attenuation of the virus in cords suspended in Pasteur flasks is achieved by proteolysis.

In almost every country the classical method of Pasteur and the dilution method of Högyes have been replaced by the use of etherized and, especially, phenolized vaccines, which retain their immunizing properties for months, can be despatched to places far from their place of manufacture and with which immunization can be effected in hospitals, dispensaries or even in the houses of the physician or of the bitten person.

Anti-rabies serum has failed in practice to fulfil the hopes to which it originally gave rise.

By reason, perhaps, of the period of "neurotropism", through which we are now passing, the number of paralytic accidents complicating anti-rabies treatment is on the increase. In this connexion it is important to distinguish between "*rage de laboratoire*", where the virus used in treatment is recovered on autopsy, and the rightly termed "paralytic accidents" which, though usually less serious, are much more frequent.

Failures of treatment should not be concealed any more than the neuro-paralytic accidents of treatment. Often they result from an inadequate amount of vaccine employed. Blame must be laid not on Pasteurian treatment

but on its application. What is the position? Mild treatment followed by failure? Intensive treatment complicated by paralytic accident? No; it is when mild treatment is administered that both failures and paralytic accidents most commonly occur. In the authors' view definite proof of the efficacy of anti-rabies treatment would be furnished by success in cases bitten by rabid wolves.

Animals have also benefited by Pasteur's discovery. Almost everywhere, dogs are now being immunized with phenolized, etherized or formolized vaccines; they are no longer destroyed but are vaccinated afresh, when bitten by or after contact with, an animal showing signs or suspected of rabies. So also, in most countries, cattle, horses, sheep, pigs and goats are being successfully immunized *after* having been bitten by rabid animals; today, especially, the saving of such animals is of the greatest economic importance.

The authors conclude by stressing the need for an international rabies conference at which the several outstanding problems on rabies could be discussed and perhaps resolved. *G. Stuart*

SELLERS, T. F. **Rabies, the Physician's Dilemma.** *Amer. J. Trop. Med.* 1948, May, v. 28, No. 3, 453–6.

Wherever rabies is endemic among dogs, the medical practitioner will sooner or later be confronted with the problem of the management of human exposures, be they real or imaginary. Two responsibilities face him, *viz.*: (*a*) the relatively simple procedure of advising and administering anti-rabies vaccine treatment to persons whose exposure has been a definite break through the skin made by the teeth of a known or suspectedly rabid animal; and (*b*) the psychological problem of rabiphobia—a far greater responsibility—whose victims far outnumber those in actual need of protection.

In this connexion the author, with a background of over 20 years' experience in the State of Georgia and as a result of his statistical analysis of the case histories of more than 50,000 persons treated there since 1925, has reached the following conclusions:

"It is not hydrophobia but rather rabiphobia which constitutes the major and most troublesome problem to the practising physician and health officer. The administration of antirabic vaccine to persons actually bitten or scratched by the teeth of known or suspectedly rabid animals is a relatively simple and justifiable procedure regardless of the outcome, in that the danger of the disease is far greater and more serious than any ill effects from the vaccine, but for exposure other than actual bites, the danger of treatment complications far exceeds that of either rabies or rabiphobia."

[Dr. Seller's thesis "that rabies is transmissible to man only by direct inoculation of the infected saliva into the flesh deep enough to come in contact with nerve tissue" may, however, be disputed. GALTIER, for example, obtained positive results by infecting experimental animals with the virus upon the superficial layers of the skin. Rubbing the virus into the scarified skin is one of the most reliable methods of inducing the disease, next to inoculation. REMLINGER induced rabies in rabbits and guineapigs by bandaging the virus upon the freshly shaven skin—a result confirmed by GALLI-VALERIO. These experiments explain the possibility of infection from insignificant bites, as well as infection following exposure without biting, as in licking.]

G. Stuart

ANSELL, I. **A Fatal Case of Myelitis after Antirabic Vaccine.** *Brit. Med. J.* 1948, Aug. 14, 338–40. [12 refs.]

A fatal case of neuroparalytic accident after anti-rabies treatment with killed carbolized vaccine is described. The patient, complaining of fever and pains

in the limbs, had been admitted to hospital 14 days after having been bitten by a healthy puppy and on the date when he had received 12 anti-rabies injections, starting 2 days after the bite, and when, the animal having remained healthy, treatment had been discontinued.

During the 5 days in hospital before his death the patient, whose abdomen showed angry red indurated areas at the sites of the inoculations, developed an ascending paralysis, which finally involved the muscles of deglutition. Incidentally, the patient's family history with regard to allergy was not ascertained. The necropsy report contained the diagnosis: acute disseminated myelitis extending into the brain stem.

After reviewing the several theories (virus, toxins, allergy) advanced to explain the paralyses of anti-rabies treatment, the author finds the balance of evidence weighted in favour of acquired anaphylaxis as the causative factor and concludes that a family or personal history of allergy indicates the need for preliminary skin tests for sensitivity and that if excessive local reactions occur during treatment the desirability of desensitization should be considered.

[These views are identical with those previously expressed by HORACK (this *Bulletin*, 1939, v. 36, 730) and by THOMAS (*ibid*, 1945, v. 42, 168). It has to be observed that erythematous patches at the sites of inoculation by no means occur in all persons treated; the proportion of such reactions appears to vary in the experience of different institutes from one person in two to one in ten. And cases of paralysis have been recorded in which no special sensitivity to the anti-rabies vaccine was noted during the course of the injections.]

Apparently impressed by the experimental work of KABAT, WOLF & BEZER (*J. Exper. Med.*, 1947, v. 85, 117), who believe the antigen evoking the paralytic response to be bound up with the myelin portion of the brain tissue, the author advocates that, in order to reduce the incidence of paralytic accidents in the future, methods by which the amount of myelin tissue in anti-rabies vaccines could be reduced to a minimum should be sought and perfected.

G. Stuart

BELVERE, L. Profilassi della rabbia. [**Rabies Prophylaxis.**] *Notiziario dell'Amministrazione Sanitaria.* 1948, Apr., v. 1, No. 4, 113–14.

In Italy the progressive increase of rabies infections in both man and animals is evidenced by the fact that: (*a*) in the 8-years period 1940–47 the numbers of human cases reported annually were successively 6, 10, 22, 48, 42, 50, 25 and 54; and (*b*) in the period 1945–47 the annual numbers of bites inflicted by known, or suspectedly, rabid animals totalled 4,392, 8,202 and 16,234.

In view of the serious epidemiological situation thus created, the Central Health Authority has instructed local administrations to reorganize their anti-rabies services both as regards prophylactic vaccination and measures of control generally.

Anti-rabies institutes are being adequately staffed and equipped, observation kennels for biting animals are under construction, preparations for a census of the taxable dog population are in train, while education of the public as a whole, but especially of dog owners and bitten persons, is being catered for through the medium of newspapers, schools, posters and handbills.

The type of country-wide propaganda in this respect follows traditional lines.

G. Stuart

MALARIA

World Health Organization. Interim Commission. **Expert Committee on Malaria. Report of Second Session. Washington, D.C. May 19–25, 1948.** 50 mimeographed pp. [W.H.O. IC/205. W.H.O. IC/Mal/25, 8 June, 1948.]

The report of this session of the WHO Expert Committee on Malaria is important, as would be expected. The members were Gabaldon, Covell, Russell, Vaucel, Viswanathan and Pampana, assisted by Afridi, Field, Bagster Wilson, Aykroyd, Alvarado, Antunes, Vargas, Coatney, Huff, Soper and Stage.

The report is divided into 10 sections, the first of which is an introduction, and the second a very brief statement on world needs. Section 3 deals with WHO malaria policy, which is to assist governments to accomplish effective malaria control, through WHO regional organizations; it is concerned with programmes and machinery for control, training, the spreading of knowledge, the development of uniform procedure and nomenclature and the promotion of measures to protect countries against the introduction of anophelines from the outside.

Examples are given of different existing antimalarial organizations such as those established in India and certain South American countries, the emphasis being on elasticity. Training involves instruction of three grades of staff—directive professional staff, assistant professional staff, and subordinate personnel—and it includes the means for making available to them the latest information from all over the world. Individual experts and operational demonstration teams "should primarily demonstrate the use of residual insecticide spraying as a method of malaria control." Three teams should be formed as early as possible, to be allocated, on request, to Central Africa, South-East Asia and Tropical America.

The general public must be educated, but the most effective propaganda is successful demonstration of practical malaria control.

In section 4, on Agriculture and Malaria, there is a provisional memorandum prepared by the FAO in which are discussed such matters as the effects on agricultural production of ill-health due to malaria, and the possibility that malaria may be introduced into an area as a result of change due to human or natural agencies, for instance irrigation [a possibility which may also apply to schistosomiasis].

Section 5 is devoted to the use of insecticides, of which DDT is the most satisfactory. Benzene hexachloride has a shorter residual action and a disagreeable odour; DDD and TDE (tetrachloro-diphenylethane) are useful larvicides where the safety of fish needs consideration; chlordane and chlorinated camphene do not possess as long an effective residual action as DDT; combinations of pyrethrum with piperine compounds increase the effectiveness of the pyrethrum, but need more investigation; parathion is toxic for warm-blooded animals.

The committee expresses the opinion that there is definite and overwhelming evidence that modern insecticides, properly applied, can be relied upon to produce a significant reduction in malaria morbidity, though doubt has been expressed in Africa as to the efficacy of DDT on *Anopheles gambiae*, and more work is needed.

The effective dose of DDT used as a residual spray against adult anophelines varies in different circumstances from 60 to 200 mgm. per square foot, and the optimum frequency of spraying from once in 6 weeks to once in 12 months. Many factors must be taken into account, including the composition of the surface to be sprayed, and the habits of the mosquitoes concerned, before

rules can satisfactorily be laid down for any particular work. As larvicides the new compounds are very effective, and for DDT the effective dose is 6 quarts of a one per cent. solution in kerosene or fuel oil per acre of stagnant water, and one part of DDT per million of water in running streams. Details are given of other formulations. In rural communities residual-spray-killing of adult anophelines is usually more economical than the use of larvicides, but this may not be so in urban centres. For species which rest indoors, residual spray may be enough, but for those which tend to rest outside, after feeding indoors, anti-larval methods are needed also.

In section 6, on chemotherapeutics in malaria control, the committee accepts the proposition that in the existing state of knowledge measures against mosquito transmission are the only methods giving permanent control of malaria, but agree that chemotherapy and chemoprophylaxis are important in the clinical control of epidemic malaria, and that the latter, though secondary, is important for personal protection. Suppressive drugs are particularly useful for collections of workmen, for armies in the field, and for certain other groups.

Further information is needed on the results of taking synthetic drugs for many years, and on their effect on the state of immunity of people living in highly endemic conditions.

The various drugs in common use are discussed in some detail, and courses commonly used in treatment are quoted, for instance :—

Mepacrine

	1st day	2nd day	Succeeding days	Total
Non-immunes	1·0	0·3	0·3 × 5 days	2·8 gm.
	0·9	0·6	0·3 × 5 ,,	3·0 ,,
	0·6	0·6	0·3 × 5 ,,	2·7 ,,
Partial immunes ...	0·6	0·3	0·3 × 3 ,,	1·8 ,,

These amounts are for adults and are administered in three or more daily doses.

The optimum suppressive dose for non-immunes is 0·1 gm. daily; a preliminary build-up of 0·3 gm. daily for five days is sometimes advocated.

Chloroquine

American experience indicates that the optimal adult dosage, *expressed as base,* is as follows :—

	1st day	Succeeding days	Total
U.S.A. ...	0·6 gm. (divided in two doses)	0·3 gm. daily for three days	1·5 gm.
Venezuela	0·9 gm. (divided in three doses)	0·9 gm. on second day only in three doses	1·8 gm.

N.B.—The tablets of 0·25 gm. of chloroquine diphosphate contain 0·155 gm. of base.

For suppression 0·3 gm. of base (0·5 gm. of chloroquine diphosphate) is given once each week.

Paludrine

There is such wide difference in the effective range of dosage that the indications which follow must be regarded as provisional:

(*a*) For standard therapy, in adults: paludrine monohydrochloride, 0·3 gm. daily for five to ten days (the monohydrochloride contains 86·5 per cent. of paludrine base).

(*b*) For single dose therapy, in adults: 0·3 gm. of monohydrochloride in one dose, followed by a weekly suppressive dose of 0·1 gm. to 0·3 gm. on the same day of the week.

The single dose method is not recommended for routine hospital treatment of *P. falciparum* malaria with paludrine. The committee notes that the best results with paludrine as a preventive have been obtained in the Far East, where 0·3 gm. given on one day each week may be enough, but in other parts of the world, and with other strains of *P. falciparum*, this dosage may be insufficient [a daily dose of 0·1 gm. has, in fact, been advocated in West Africa, see WALLS, below].

The gametocides plasmoquine, pentaquine and iso-pentaquine are considered briefly.

In section 7, on research, a number of examples are given of studies which need to be undertaken either as basic research or as applied research. These examples are not discussed. and should be sought in the original by those proposing to initiate research.

Section 8 is concerned with quarantine, especially with regulations for the disinsectization of ships and aircraft which may introduce anophelines into countries which the authorities desire to protect; this section should be read in the original.

Sections 9 and 10 deal with recommended resolutions, and with conclusions and recommendations.

[The report as a whole represents a careful essay on some aspects of malaria control, which should be closely studied by governments and medical organizations in the tropics. A basic assumption is made that malaria causes ill-health, without much differentiation between the disability experienced in conditions of seasonal transmission and in those of perennial transmission with a resulting high degree of immunity in adults. The extent of malarial illness in the indigenous people of countries showing these degrees of transmission is not yet fully understood (and the Committee suggests research on the subject), and the effect of the various methods of control on communities subject to hyperendemic conditions is not satisfactorily known. Obviously, if control is perfect and permanent, there would be no malaria, but partial control only is possible in many places, and this may produce unexpected results. It would seem necessary that a long-term observation should be carried out to attempt to assess the health importance of malaria in the various conditions of transmission, and of the effects of partial control in hyperendemic areas. The committee lays great stress on residual insecticides, and little stress on the older methods of drainage, water-control, biological control, etc., but it may be possible, as the committee admits, that races of anophelines not so susceptible to the action of insecticides (though none has yet been found), or having resting habits which do not bring them into contact with sprayed surfaces, will be selected out, to replace those which now transmit the disease. It would be unwise to lose sight of the well-tried methods, and the committee has probably no intention of doing so.] *Charles Wilcocks*

*Alving, A. S., Craige, B., Jr., Pullman, T. N., Whorton, C. M., Jones, R., Jr. & Eichelberger, Lillian. **Procedures used at Stateville Penitentiary for the Testing of Potential Antimalarial Agents.** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 2–5.

About 500 inmates of the Illinois State Penitentiary at Stateville volunteered to act as subjects for the controlled clinical testing of new antimalarial drugs. The results of studies already completed are set out in this special malaria supplement of the *Journal of Clinical Investigation.* The primary object of the studies was to obtain information about the effect of potential antimalarial drugs upon the relapse rate of sporozoite-induced *P. vivax* malaria. The prophylactic and suppressive effects of the drugs were also studied, and observations were made on their toxicology and pharmacology.

All the subjects were white males in good physical health between the ages of 21 and 40 ; none had lived in a known malarious area and none had a history suggestive of previous malaria infection. There is no endemic malaria in Stateville. The Chesson strain (New Guinea) of *P. vivax* malaria was used. This strain is characterized by a high relapse rate when such drugs as quinine or mepacrine are used in treatment, and by the almost complete absence of delayed primary attacks.

Anopheles quadrimaculatus was used for the transmission of infection. Each patient received the bites of ten infected mosquitoes. In the standard prophylactic procedure the drug to be tested was administered on the day before infection, on the day of infection, and on each of the following six days. Thick films of the peripheral blood were taken daily after the eighth day following inoculation.

In the curative tests the drugs were administered at intervals of four hours to obtain fairly constant concentrations in the body fluids. Slowly excreted drugs such as quinacrine, chloroquine and SN-8617 were given less frequently. The usual period of drug administration was 14 days.

Most of the drugs tested were members of the 8-aminoquinoline group of compounds : for these the usual observations of temperature, blood pressure, urine analysis, and plasma drug concentrations, were supplemented by a leucocyte count every day and a differential count every fourth day ; haemoglobin and methaemoglobin determination every day, and electrocardiogram after treatment. *Norman White*

Jones, R., Jr., Craige, B., Jr., Alving, A. S., Whorton, C. M., Pullman, T. N. & Eichelberger, Lillian. **A Study of the Prophylactic Effectiveness of several 8-Aminoquinolines in Sporozoite-induced *Vivax* Malaria (Chesson Strain).** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 6–11. [18 refs.]

The four compounds studied, pamaquin, SN-11,191, SN-1,452 and SN-13,276 (pentaquine) are all 6-methoxy-8-aminoquinolines. They all have high antimalarial activity in avian infections and their toxicity in the monkey is low. The methods of infection and drug administration are described above. Pamaquin 90 mgm. [Pamaquin base] a day for 8 days beginning the day before inoculation protected two of five patients from infection ; they exhibited no sign of malaria during 20 months of observation. Two developed fever and parasitaemia 18 and 19 days after sporozoite inoculation. One developed a delayed primary attack of malaria 106 days after infection.

*This and the following 21 abstracts represent summaries of a symposium on malaria which occupied a complete number of the relevant journal. They are therefore presented together, in the order in which they appeared.

Two of three subjects treated with SN-11,191 (90 mgm. a day) and two treated with SN-1,452 (240 mgm. a day) had no malaria during 20 months of observation. One subject in each of these two groups developed malaria within 3 weeks of inoculation.

The four subjects who served as controls for these first three drugs tested developed clinical malaria 12 to 14 days after inoculation.

One of five subjects treated with pentaquine (120 mgm. a day) developed fever and parasitaemia 22 days after inoculation. The other four have shown no evidence of malaria during 9 to 11 months of observation. The 12 control subjects for this experiment all developed clinical malaria in 12 to 19 days.

All of five patients receiving 180 mgm. of pentaquine a day remained free from malaria during nine months of observation although two of them received the drug for only two days and two others for only three days after the day of inoculation. The ten controls for this experiment all developed malaria 12 to 17 days after inoculation.

All doses mentioned above are in terms of base weight.

As the drugs were used in doses approaching the estimated maximum tolerated dose, signs of toxicity were expected and found. Epigastric discomfort or pain (most severe in patients taking 180 mgm. SN-13,276), anorexia, nausea and vomiting were noted. Cyanosis was noted when the methaemoglobin exceeded 6 or 7 per cent. of the total haemoglobin. The average loss of haemoglobin was 1·75 gm. per 100 ml. of blood, the greatest loss being about the 12th to 14th day after the start of medication.

The results show that all four drugs may act as true prophylactics for sporozoite-induced *P. vivax* malaria, but they did not protect all subjects. There was no positive correlation between plasma drug concentration and the prophylactic effect of these drugs. In subjects whose primary attacks of malaria were not prevented, the disease was so altered by the prophylactic treatment that it was rendered susceptible to cure by drugs ordinarily incapable of preventing relapse. It would seem that these drugs exert a deleterious effect upon pre-erythrocytic stages of the malaria parasite. Their relatively high toxicity precludes their general use as prophylactics. *Norman White*

PULLMAN, T. N., EICHELBERGER, Lillian, ALVING, A. S., JONES, R., Jr., CRAIGE, B., Jr. & WHORTON, C. M. **The Use of SN-10,275 in the Prophylaxis and Treatment of Sporozoite-induced *Vivax* Malaria (Chesson Strain).** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 12–16, 3 figs. [14 refs.]

SN–10,275 is 6,8-dichloro-2-phenyl-α-2-piperidyl-4-quinolinemethanol and has a close chemical similarity to quinine. Three subjects receiving 0·859 gm. (of base) a day for 8 days beginning the day prior to inoculation developed fever and parasitaemia, but the prepatent periods were from 6 to 9 times longer than in three control subjects. The plasma concentrations at the time of appearance of parasitaemia ranged from 66 to 110 gamma per litre.

After treatment with SN–10,275, the latent periods of those who relapsed were 296, 107 and 99 days. The median latent periods observed with quinine and quinacrine in the Chesson strain of malaria under the conditions of this investigation were 15 and 34 days respectively.

SN–10,275 remained in the plasma for long periods after medication was stopped. There was a wide variation in the rate of fall; the mean loss for the majority of the group was 20 per cent. per week, a much lower rate of disappearance than that shown by quinine or quinacrine [mepacrine].

Eight patients received SN–10,275 at a dosage of 1·0 gm. of the salt a day. One had mild gastro-intestinal symptoms, cramps, nausea and mild diarrhoea.

Another had fever of 102°F., headache and backache at the end of the 14-day course of treatment. All eight patients had photosensitivity of the skin, from a slight tingling of the face to severe burning sensations with erythema. One had some desquamation of the skin of the nose and another mild labial oedema. These symptoms appeared only after exposure to sunlight. The severity and duration of these symptoms are roughly correlated with the mean concentration of SN–10,275 in the plasma.

Toxic reactions and the variation in the rate of disappearance of the drug from the body limit the value of SN–10,275 as a suppressive drug, but further investigation of related compounds is indicated because a non-toxic drug with the antimalaria activity of SN–10,275 which remained in the body for long periods of time would have great value in the suppression of malaria.

Norman White

Craige, B., Jr., Eichelberger, Lillian, Jones, R., Jr., Alving, A. S., Pullman, T. N. & Whorton, C. M. **The Toxicity of Large Doses of Pentaquine (SN–13,276), a New Antimalarial Drug.** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 17–24, 4 figs. [16 refs.]

The purpose of the observations reported in this paper was to define the margin of safety of pentaquine (SN–13,276) in the treatment of malaria. In the therapeutic trials, five subjects received 120 mgm. pentaquine base a day with quinine for 14 days. Five others received similar treatment but without quinine. In the prophylactic trials, five subjects received 120 mgm. pentaquine base a day for eight days, and five 180 mgm. a day for eight days. The doses used were double or treble the amounts necessary for antimalarial treatment.

The toxic reactions were severe. Most of the subjects had severe abdominal pain, nausea, anorexia and methaemoglobinaemia, similar to the symptoms produced by toxic doses of pamaquin. Serious physiological abnormalities developed in three of the subjects taking 120 mgm. of pentaquine a day without quinine, therapeutically. They displayed postural hypotension with syncope, arterial and venous oxygen unsaturation, and loss of weight, which persisted for a long time after the end of treatment. The symptoms were possibly due to central impairment of the sympathetic nervous system.

Norman White

Alving, A. S., Craige, B., Jr., Jones, R., Jr., Whorton, C. M., Pullman, T. N. & Eichelberger, Lillian. **Pentaquine (SN–13,276), a Therapeutic Agent effective in reducing the Relapse Rate in *Vivax* Malaria.** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 25–33, 2 figs. [14 refs.]

The procedure adopted at the Illinois State Penitentiary for the testing of antimalarial drugs has been described above. In spite of efforts to secure uniformity in the induced disease, variations occurred. It was possible, however, to distinguish severe from less severe infections according to the length of the prepatent or preceding latent periods. Subjects with long prepatent or latent periods had a relapse rate of 67 per cent. after treatment with so-called suppressive drugs: those with short periods a relapse rate of 98 per cent. A small group of volunteers had massive infections, being bitten by 80 infected mosquitoes instead of the ten used in the standard procedure: their relapse rate was 100 per cent. The subjects were accordingly divided into three categories representing a moderate, a severe and an extremely severe challenge to the therapeutic efficiency of the test drug.

Pentaquine was given to 82 persons in daily doses of 60 mgm. of base or less for 14 days. When it was given alone in doses of 30 or 60 mgm. a day, fever disappeared in two to four days; parasites disappeared in three to six days. Twenty-six moderately infected subjects were given 60 mgm. a day and four others 30 or 45 mgm. a day. These 30 subjects also received 2 gm. quinine sulphate daily. The relapse rate was only 3 per cent. as compared with 67 per cent. obtained when similar cases are treated with suppressive drugs. Of 21 subjects with severe infections treated with pentaquine alone in doses of 15 to 45 mgm. of base a day, all but one relapsed. Pentaquine 60 mgm. a day reduced the relapse rate of severely infected patients; only two of four relapsed. Seventeen severely infected subjects received this daily dose of pentaquine with 2 gm. quinine sulphate, for fourteen days; only three relapsed—a reduction in the relapse rate from 98 to 18 per cent. The extremely heavy infections all relapsed after pentaquine treatment.

Pentaquine should only be administered under close medical supervision. The daily dose of 60 mgm. should not be exceeded; this has the same toxicity as 30 mgm. of pamaquin base or 67 mgm. of its naphthoate salt. The toxicity of pentaquine is too great to warrant its use in prophylaxis or prolonged suppression. *Norman White*

ALVING, A. S., PULLMAN, T. N., CRAIGE, B., Jr., JONES, R., Jr., WHORTON, C. M. & EICHELBERGER, Lillian. **The Clinical Trial of Eighteen Analogues of Pamaquin (Plasmochin) in *Vivax* Malaria (Chesson Strain.)** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 34–45, 4 figs. [25 refs.]

This is a record of work done in the search for a drug possessing the capacity of pamaquin to reduce the relapse rate of *vivax* malaria, but devoid of the toxic properties of that drug which hamper its extended use. The observations were made in the Illinois State Penitentiary: the procedure adopted is described above. Only pamaquin analogues with pamaquin-type toxicity in animals were used. They had previously been tested for antimalarial activity in avian infections and for toxicity in rodents, dogs and monkeys.

The eighteen 8-aminoquinolines tested were: SN-191, SN-9,972, SN-11,191, SN-12,325, SN-12,352, SN-12,354, SN-12,451, SN-13,232, SN-13,233, SN-13,274, SN-13,276, SN-13,380, SN-13,429, SN-13,619, SN-13,694, SN-13,697, SN-14,011 and DR-15,302. It was at first planned to administer the maximum tolerated dose as estimated from the animal experiments. Severe toxic reactions caused by four of these drugs at this high dosage led to the abandonment of this plan. Thereafter $\frac{1}{6}$ of the estimated maximum tolerated dose was administered; if toxicity for man was found to be absent, or mild, larger doses were tried.

Drugs were administered in equal doses every four hours over a period of fourteen days. Quinine was administered concurrently with the drugs, 2 gm. of the sulphate or dihydrochloride daily.

Eight of the drugs were ineffective in preventing relapse of severe infections, in the doses used. Ten compounds apparently cured one or more patients with severe infections. Five exhibited pronounced activity inasmuch as the majority of patients treated with them had not subsequently relapsed (follow-up period from two months to one year). These drugs are SN-9,972, SN-13,274, SN-13,429, DR-15,302 and SN-13,276 (pentaquine).

No serious toxic symptoms were caused by any of the drugs on the reduced dosage: the most common symptoms were abdominal pain, nausea and vomiting. Cyanosis occurred when methaemoglobinaemia exceeded 5 or 6 per cent. of total haemoglobin. Mild drug fever, leucocytosis and leucopenia have been observed.

The studies indicate that the curative properties of pamaquin are shared by several analogues, but no definite conclusions can be drawn as to the specific molecular configuration required in a curative drug.

Drug régimes which produced a high percentage of cures tended to prolong the subsequent latent periods in patients whom they failed to cure.

Norman White

PULLMAN, T. N., CRAIGE, B., Jr., ALVING, A. S., WHORTON, C. M., JONES, R., Jr., & EICHELBERGER, Lillian. **Comparison of Chloroquine, Quinacrine (Atabrine), and Quinine in the Treatment of Acute Attacks of Sporozoite-induced *Vivax* Malaria (Chesson Strain). Preliminary Report.** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 46–50, 2 figs. [15 refs.]

The antimalarial chloroquine (7-chloro-4-(4-diethylamino-1-methyl-butyl-amino)-quinoline) was synthesized during the late war in U.S.A. Its activity was reported on by LOEB *et al.* [this *Bulletin*, 1946, v. 43, 708], and has now been compared with that of quinine and quinacrine (atebrin, mepacrine), under controlled conditions, in the treatment of primary attacks and early relapses of sporozoite-induced *P. vivax* malaria of S. Pacific origin (Chesson strain). For this purpose, 39 prisoner-volunteers were infected by the bites of 10 *Anopheles quadrimaculatus* or by injection of sporozoites from their salivary glands. Treatment was begun early in the attacks. On the first day, 0·8 gm. chloroquine base was given, followed by 0·2 gm. daily for 6 days (total 2·0 gm. over one week). In the same period approximately 2·7 gm. atebrin base and 11 to 12 gm. quinine base were administered (or 21 to 23 gm. of quinine base over 14 days) to different groups. The dosage approached the maximum which was well tolerated. Plasma levels of each drug were measured by the methods of BRODIE & UDENFRIEND [this *Bulletin*, 1943, v. 40, 821 ; 1944, v. 41, 453 ; 1947, v. 44, 793].

Parasites were generally removed from the blood most rapidly by chloroquine. The relapse rate for each drug was 90 per cent. or over. The latent interval after drug administration was longest after chloroquine treatment, possibly owing to its slower excretion or degradation, or to the greater margin between minimal effective plasma level and that reached by the above dosage. The drug proved superior to quinine and atebrin under the conditions employed.

J. D. Fulton

JONES, R., Jr., PULLMAN, T. N., WHORTON, C. M., CRAIGE, B., Jr., ALVING, A. S. & EICHELBERGER, Lillian. **The Therapeutic Effectiveness of Large Doses of Paludrine in Acute Attacks of Sporozoite-induced *Vivax* Malaria (Chesson Strain).** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 51–5, 2 figs. [17 refs.]

Reports on the treatment of *P. vivax* and *P. falciparum* infections with paludrine have been reviewed [this *Bulletin*, 1946, v. 43, 402, 821 ; 1947, v. 44, 282 ; 1948, v. 45, 34, 238, 491]. Its value in treatment of acute attacks following sporozoite-induced infections of *P. vivax* of S.W. Pacific origin (Chesson strain, which is characterized by early onset of primary attacks, high relapse rate and short interval between attacks) has been compared with that of other suppressive drugs. The patients were healthy white prisoner-volunteers and were infected by the bites of 10 *A. quadrimaculatus* or by injection of their salivary glands. Only primary attacks or early relapses were treated so as to avoid the factor of acquired immunity, and treatment was begun at the onset of fever or detection of parasitaemia. All drugs were given by mouth, and the dosage recorded represents that of the free base. Ten

patients were treated with paludrine and received 0·97 gm. daily for 14 days in equal doses given every four hours. The dosage for quinacrine (atebrin, mepacrine) was 0·87 gm. in four equal doses on the first day and 0·35 gm. similarly divided on the following 6 days. Pentaquine (6 methoxy-8(-5 isopropylaminoamylamino)-quinoline) was given in 10 mgm. doses every 4 hours for 14 days. The method of SPINKS & TOTTEY [this *Bulletin*, 1946, v. 43, 707] was used for estimation of paludrine in plasma, and one based on that of BRODIE *et al.* [this *Bulletin*, 1947, v. 44, 793] for pentaquine.

Quinacrine was more effective in terminating acute attacks than paludrine, which cleared the blood of parasites less slowly than chloroquine (see above). When infections were severe, radical cures were not obtained with these drugs, but paludrine was a valuable drug in treatment of acute infections, and toxic effects were negligible. Some patients with less severe infections did not relapse after treatment with it or with quinine. The length of the latent period after treatment with paludrine was intermediate between that after treatment with quinine and atebrin. Neither quinine nor pentaquine exhibited synergistic activity with paludrine. *J. D. Fulton*

ALVING, A. S., EICHELBERGER, Lillian, CRAIGE, B., Jr., JONES, R., Jr., WHORTON, C. M. & PULLMAN, T. N. **Studies on the Chronic Toxicity of Chloroquine (SN-7618).** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 60–65, 4 figs. [16 refs.]

These studies were undertaken to determine whether chloroquine could be taken for long periods as a malaria suppressive without causing serious toxicity. To establish the margin of safety larger doses than those necessary for suppression were given. The subjects were inmates of the Illinois State Penitentiary free from any physical disability or neurosis. There were two groups of twenty each. The members of the first group each received 0·5 gm. chloroquine base once a week, for a year. Members of the second group were given 0·3 gm. of the base daily, in two doses, for 77 days, and then 0·5 gm. weekly, as in the first group, for the rest of the year. In the daily dosage studies, mean "low" plasma concentrations in excess of 200 gamma per litre were maintained for ten weeks. A plasma chloroquine concentration of 10 gamma per litre is sufficient for malaria suppression. Individual "low" values in excess of 500 gamma per litre occurred without unusual symptoms.

On the higher dosage, visual disturbances, headache, bleaching of the hair, electrocardiographic changes and slight loss of weight occurred. These symptoms are said to have caused no incapacity, and they diminished or disappeared when the dose was reduced. Members of the group on the weekly dose suffered from occasional headaches and lost a little weight. Two had a skin eruption resembling lichen planus.

It is concluded that chloroquine is a safe antimalarial preparation when given in the recommended dosage. The dosage recommended for the treatment of an acute attack of *vivax* or *falciparum* malaria is 1·5 gm. of chloroquine base in three days: for suppression 0·3 gm. a week. *Norman White*

SHANNON, J. A., EARLE, D. P., Jr., BERLINER, R. W. & TAGGART, J. V. **Studies on the Chemotherapy of the Human Malarias. I. Method for the Quantitative Assay of Suppressive Antimalarial Action in Vivax Malaria.** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 66–74, 4 figs.

It has now been demonstrated by SHORTT and GARNHAM [this *Bulletin*, 1948, v. 45, 762] that in sporozoite-induced *P. vivax* malaria and in infections with *P. cynomolgi* in monkeys a tissue phase of the infection occurs. From the

persistent tissue phase erythrocytic forms may arise and thus bring about relapses. This tissue phase is absent in blood-induced infections and relapses do not occur. The activity of drugs has been classified as prophylactic, suppressive or curative, depending on the effects produced. The practical needs of war created a demand for active suppressive agents, and for assessment of their value blood-induced infections were widely used. The authors have investigated the validity of this procedure and have tested the susceptibility to quinine of the red cell forms which arise from inoculation of infected blood as well as from sporozoite inoculation. The susceptibility of different strains of the same plasmodium to this drug was also investigated. For this purpose standardization of conditions with regard to host and parasite were necessary in order to obtain reliable results.

White syphilitic patients with central nervous system involvement, having no previous history of malaria and therefore presumed to be susceptible, were employed. In the earlier experiments, the McCoy strain of *P. vivax* was used and its biological characters are described. Thirty patients were inoculated with 500,000 parasites from an early primary infection and the course of parasitaemia was followed in blood smears. Therapy was started on the fourth or fifth day of fever and drug dosage was arranged to give a constant plasma level for 4 days. Estimations were made by the method of BRODIE & UDENFRIEND [this *Bulletin*, 1943, v. 40, 821]. If blood smears became negative as the result of treatment, observation was continued over a period of 14 days, and if still negative reinoculation with twice the original number of parasites was carried out and observation continued for another period of 14 days.

The results of therapeutic treatment could be arranged into three classes. In the first, the drug was without effect, in the second a temporary effect was obtained with partial or complete disappearance of parasitaemia and fever, followed by recurrence within a specified period. In the third class, there was complete disappearance of parasites and the patient became susceptible to inoculation. The three classes were correlated with mean quinine plasma concentrations, indicating "that the susceptibility to quinine is a stable characteristic of the infective organism." The correlation between plasma-quinine levels and therapeutic effect was greater than between oral dosage and effect. The result obtained with a given drug concentration was independent of the degree of parasitaemia. Those obtained by similar treatment of 15 patients infected with the same strain of parasite by means of sporozoites indicated that the action of quinine against the resulting blood forms did not differ from its action against the same forms derived from blood inoculation. In similar experiments the Chesson strain of *vivax* malaria of New Guinea origin appeared to possess greater resistance to quinine than the McCoy strain. Certain characters of the Chesson strain are of special value in blood-induced infections for indicating the resistance of red cell forms to chemotherapeutic agents. [This important paper should be consulted in the original by those interested.]

J. D. Fulton

EARLE, D. P., Jr., BERLINER, R. W., TAGGART, J. V., WELCH, W. J., ZUBROD, C. G., WISE, Nancy B., CHALMERS, T. C., GREIF, R. L. & SHANNON, J. A. **Studies on the Chemotherapy of the Human Malarias. II. Method for the Quantitative Assay of Suppressive Antimalaria Action in Falciparum Malaria.** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 75–9.

In continuation of the work described in Part I of the series dealing with *P. vivax* [above], the susceptibility of the erythrocytic forms of 2 strains of *P. falciparum* to quinine has now been investigated as a basis for the assessment

of antimalarial activity. Similar studies projected for *P. malariae* had to be abandoned on account of practical difficulties. The patients as before were neurosyphilitics carefully chosen, and received an intravenous inoculation of 500,000 erythrocytic forms of the potentially virulent McLendon strain of *P. falciparum* from an untreated patient on the first or second day of fever, and the course of the infection was followed in blood smears. Therapy was begun early in the infection to avoid danger to life. A loading dose of quinine was followed by others at 4- to 6-hour intervals in order to maintain a constant plasma concentration over a period of 4 to 8 days, which was checked by frequent drug estimations. After completion of the dosage schedule, observation was started on the day after the final effective plasma level and was continued for 21 days in the event of disappearance of parasitaemia and fever. Reinoculation with twice the original number of parasites was then carried out and observations were continued till parasites reappeared.

The therapeutic results were arranged in three classes as in the earlier experiments. In the 34 patients investigated, the results indicated that the therapeutic response to quinine was correlated with the duration of therapy (longer than in the experiments with *P. vivax*) and with the plasma quinine concentration. In similar experiments with another strain of *P. falciparum* (Costa strain) 21 patients were similarly investigated. The latter strain gives rise to a clinical picture like the other, but the erythrocytic parasites from blood- and sporozoite-induced infections nevertheless appeared to be more resistant to the suppressive action of quinine. The strains of *P. falciparum* employed showed greater resistance than the *P. vivax* strains to the suppressive action of this drug when judged in terms of plasma concentration. *J. D. Fulton*

TAGGART, J. V., EARLE, D. P., JR., BERLINER, R. W., ZUBROD, C. G., WELCH, W. J., WISE, Nancy B., SCHROEDER, E. F., LONDON, I. M. & SHANNON, J. A. **Studies on the Chemotherapy of the Human Malarias. III. The Physiological Disposition and Antimalarial Activity of the Cinchona Alkaloids.** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 80–86. [18 refs.]

Quinine has been the most widely used of the four chief cinchona alkaloids in the treatment of malaria, in spite of the fact that experiment has shown the others to possess comparable activity. On account of war needs, further investigations were undertaken since supplies of cinchona bark containing the alkaloids other than quinine were readily available in the Western hemisphere. The present studies deal with the distribution, activity and toxicity of the four principal cinchona alkaloids in a quantitative manner, with the aim of establishing a rational basis for their employment. The well-known methods of BRODIE & UDENFRIEND [this *Bulletin*, 1943, v. 40, 821 ; 1947, v. 44, 793] were used for their estimation in biological fluids. The therapeutic tests and classification of results were similar to those employed in Parts I and II of this series [above]. Particular attention was paid to the relationship between oral dosage and resulting plasma concentration. Absorption, distribution, degradation and excretion were also studied after oral administration in soft gelatin capsules over a period of 4 to 6 days.

It was found that the plasma concentration resulting from a particular dosage of any of the alkaloids varied widely in different individuals. The highest levels were attained with quinine and were lowest with cinchonine, probably because the latter was largely metabolized rather than because of its deposition in tissues. Peak values were reached with a single dose by mouth within 3 hours, but persisted for a short time only, and soluble salts produced a higher

level than the alkaloidal bases. Maintenance doses of each, however, gave rise to the same equilibrium plasma concentration. Absorption from the gastrointestinal tract was almost complete as judged by the small amount of material excreted in faeces (less than 5 per cent.), which consisted mostly of unchanged alkaloids. The concentration of quinine and cinchonine in plasma was more than 5 times that in the blood cells. In animals it has been shown [this *Bulletin*, 1944, v. 41, 11 ; 1945, v. 42, 778] that the concentration of these substances in organs and tissues is many times that in plasma. In man there appears to be little localization in tissues and no cumulative effect. Only a small percentage of the administered dose was excreted unchanged in the urine. The percentage of degradation products so excreted varied widely for the different alkaloids. Renal excretion plays only a minor part in regulating plasma concentrations of the parent substances, and in the body they undergo metabolic alteration to a large extent. One of the chief products formed in each case is the 2-hydroxyquinoline derivative, first isolated from quinine by KELSEY *et al.* [this *Bulletin*, 1944, v. 41, 923]. The derivative from cinchonine was shown to possess very little antimalarial activity. KNOX [this *Bulletin*, 1946, v. 43, 1005] showed that an enzyme from rabbit liver could bring about a similar oxidation in all four alkaloids, but there is no evidence that the same enzyme is responsible for the oxidation in man.

The plasma concentration required to interrupt *P. vivax* or *P. falciparum* infections varied with each alkaloid, but the antimalarial activities of the four alkaloids did not differ widely. Cinchonine, however, showed a lesser activity against one strain of *P. falciparum*. Cinchonism was encountered with quinine, and other unpleasant side-effects occurred with cinchonine, but only one patient showed idiosyncrasy to the former. It appears from the results obtained that any one of the four alkaloids is effective in control of clinical attacks of malaria, provided that doses are given every 6 hours in order to maintain effective plasma drug levels. On account of their excretion and metabolism, these cinchona products are probably not so effective for suppression as some newer drugs with different distribution in the body. *J. D. Fulton*

EARLE, D. P., Jr., WELCH, W. J. & SHANNON, J. A. **Studies on the Chemotherapy of the Human Malarias. IV. The Metabolism of Cinchonine in relation to its Antimalarial Activity.** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 87–92. [12 refs.]

The metabolic changes which a drug undergoes in the body may be of significance for the chemotherapeutic effect which it exerts. An investigation was undertaken from this viewpoint with cinchonine since it is known to undergo considerable metabolic changes in the animal body. KELSEY *et al.* have carried out investigations in this field [this *Bulletin*, 1944, v. 41, 11, 260 ; 1946, v. 43, 404] while MEAD and KOEPFLI [*ibid.*, 1945, v. 42, 9] showed that the substance obtained from quinine was the 2-hydroxy derivative. KNOX [this *Bulletin*, 1946, v. 43, 1005] showed that there is an enzyme in rabbit liver which can oxidize the four chief cinchona alkaloids to a similar derivative.

Most of the present data was obtained from normal patients. With the use of the method of FISHER *et al.* (*J. Pharm. & Exper. Therap.*, 1943, v. 79, 373) the amount of cinchonine and its 2-hydroxy derivative bound to albumin was found to be considerable. Absorption from the intestinal tract of the two substances was almost complete. From the urine, less than 5 per cent. of the parent substance was recovered and more than 50 per cent. of the 2-hydroxy derivative. The relationship between oral dosage and the blood plasma concentrations of each was determined by the well-known methods of BRODIE and UDENFRIEND

[this *Bulletin*, 1947, v. 44, 793]. Results showed that when the parent substance or equal amounts of the two substances were given orally the resulting concentration of the derivative was greater in each case and its renal clearance was higher than that of cinchonine itself and was not depressed by doses of alkali to the extent that occurs with other organic bases. These differences were due largely to the greater rate of metabolism of cinchonine. The metabolic product was considerably less active than the parent substance against the McCoy strain of *P. vivax* when judged on the basis of plasma concentrations attained. *J. D. Fulton*

TAGGART, J. V., EARLE, D. P., Jr., BERLINER, R. W., WELCH, W. J., ZUBROD, C. G., JAILER, J. W., KUHN, Beatrice H., NORWOOD, J. & SHANNON, J. A. **Studies on the Chemotherapy of the Human Malarias. V. The Antimalarial Activity of Quinacrine.** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 93–7, 1 fig.

As a result of the development of simple and accurate methods for the estimation of quinacrine (atebrin, mepacrine) by BRODIE and UDENFRIEND and by MASEN [this *Bulletin*, 1944, v. 41, 453 ; 1945, v. 42, 8] in biological materials, and of various studies, including those of SHANNON *et al.* [*ibid.*, 1945, v. 42, 343] on its distribution in the body, the use of this drug in suppression and treatment of malaria was put on a rational basis. This report deals with the activity of the drug in terminating acute attacks of blood-induced *P. vivax* and *P. falciparum* malaria. The methods and strains employed were those described in earlier parts of this study. Suitable priming doses were given to obtain equilibrium plasma drug levels within a few hours, and the period over which drug was given was curtailed to prevent the continuance of significant drug levels in the blood beyond the desired 4 days in the case of *vivax* malaria and 6 days in the case of *falciparum* infections. The relationship between oral dosage, plasma concentrations and therapeutic effects are considered and indicate the range of effective plasma concentrations of the drug. The results obtained should be of value when the antimalarial activity of drugs of similar character is being studied. It is clear that the results depend to some extent on the species and strain of parasite used. The adequacy of dosage schedules in current use may readily be checked but details must be consulted in the original. *J. D. Fulton*

BERLINER, R. W., EARLE, D. P., Jr., TAGGART, J. V., ZUBROD, C. G., WELCH, W. J., CONAN, N. J., BAUMAN, E., SCUDDER, S. T. & SHANNON, J. A. **Studies on the Chemotherapy of the Human Malarias. VI. The Physiological Disposition, Antimalarial Activity, and Toxicity of Several Derivatives of 4-Aminoquinoline.** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 98–107, 1 fig. [20 refs.]

Russian workers before the late war appear to have regarded 4-aminoquinoline derivatives as of value in the treatment of malaria, but do not seem to have explored this group of substances to any extent. A number of derivatives, including S.N.7618 (Chloroquine) were synthesized in America during the war and certain members of the group appeared to show greater suppressive activity than quinacrine [mepacrine, atebrin], to which they may be regarded as having some structural relationship if the latter were to suffer the loss of a benzene ring.

The present investigation deals with their physiological distribution, antimalarial activity and toxicity, and included the study of absorption from the gastro-intestinal tract, renal excretion, distribution in tissues, combination with non-diffusible constituents of plasma as well as the relationship between

oral dosage and plasma concentration. The methods of BRODIE, UDENFRIEND *et al.* [this *Bulletin*, 1947, v. 44, 793] were used for the drug estimations. It was found that absorption of these substances was practically complete after oral dosage. When equilibrium in plasma had been attained, 10 to 25 per cent. of the daily dosage was accounted for by renal excretion, which was increased by the administration of acid and decreased by alkali as previously reported. The unexcreted portion must suffer metabolic degradation. All the drugs persisted in plasma for some time after the end of treatment. The concentration of 4-aminoquinolines in the tissues of mammals was greater than in plasma. There was some localization of the drugs in red and white blood cells. As with quinacrine, these substances combined to a considerable extent with the non-diffusible elements of plasma.

In testing antimalarial activity in blood-induced infections, the McCoy strain of *P. vivax* and the McLendon strain of *P. falcpiarum* were used, as described earlier. The Chesson strain of *P. vivax* was used for mosquito-induced infections. The procedures were standardized and the results could be compared with those obtained with other drugs. As a group, the 4-aminoquinolines showed high activity against both species of malaria. The most active substances were derived from 7-chloro-4-aminoquinoline. Administration of S.N.7618 (Chloroquine) which is 7-chloro-4-(diethylamino-1-methylbutylamino)-quinoline in the dosage recommended [see this *Bulletin*, 1946, v. 43, 708] over a period of one year showed that it was a safe suppressive agent, and S.N.8137 (7-chloro-4-(3-diethylamino-2-hydroxypropylamino)-quinoline) showed similar characters and was of low toxicity. *J. D. Fulton*

BERLINER, R. W., EARLE, D. P., Jr., TAGGART, J. V., WELCH, W. J., ZUBROD, C. G., KNOWLTON, P., ATCHLEY, J. A. & SHANNON, J. A. **Studies on the Chemotherapy of the Human Malarias. VII. The Antimalarial Activity of Pamaquine.** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 108–13. [16 refs.]

Plasmoquine (pamaquin) was synthesized in Germany in 1926 by SCHULEMANN and his collaborators, and proved an active schizonticide in *P. cathemerium* infections of canaries, but did not possess the same activity in human malaria. Its most striking property was its activity against the gametocytes of *P. falciparum*. Its toxicity made it of limited value in treatment. In combination with quinine it was believed to reduce the number of relapses in benign tertian infections, SINTON [this *Bulletin*, 1930, v. 27, 656] and JAMES, NICOL & SHUTE [*ibid.*, 1931, v. 28, 973] showed that it could act as a prophylactic in mosquito-transmitted malaria.

The present authors have investigated the pharmacology and toxicity of pamaquin in order to get quantitative data on its suppressive activity in *P. vivax* and *P. falciparum* malaria and its curative action in sporozoite-induced *vivax* malaria, with a view to further development of this class of compound. Dosage was arranged to produce uniform plasma concentrations over periods of 4, 6 or 8 days, depending on the infection used, when the ability of the drug to suppress blood-induced infections was being studied. The standard method of estimation [this *Bulletin*, 1947, v. 44, 793] was employed. The suppressive action was more marked against *vivax* than against *falciparum* infections, but strain differences were apparent, and in both the drug was relatively ineffective even at high dosage. The low activity against the blood forms in *vivax* malaria made it difficult to determine whether the tissue phase of the parasite was affected. At a dosage of 60/90 mgm. daily in conjunction with 2·0 gm. quinine over a period of 14 days it had a curative action in primary infections of

sporozoite-induced *vivax* malaria (Chesson strain). There was no correlation between the plasma concentration of the drug and its suppressive or curative action. *J. D. Fulton*

ZUBROD, C. G., KENNEDY, T. J. & SHANNON, J. A. **Studies on the Chemotherapy of the Human Malarias. VIII. The Physiological Disposition of Pamaquine.** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 114–20, 2 figs.

This investigation on the physiological distribution of pamaquin (plasmoquine) was carried out with patients suffering from syphilis of the central nervous system and with normal volunteers. Since the drug is destroyed in faeces, absorption from the intestinal tract could not be studied by the normal methods, but indirect evidence was obtained from comparison of the plasma levels after a single oral and intramuscular dose that absorption was rapid and complete. The solubility of the salts used had little influence on the plasma levels reached. Peak values were higher and more rapidly attained by the intramuscular route but were not maintained for long in either case. Different persons on the same dosage schedule showed wide variations in the mean plasma levels attained. It was believed that this was due to localization rather than to difference in the rate of metabolic conversion. Experiments with dogs showed that the chief localization of the drug was in liver, lungs and brain. Indirect evidence indicated that the distribution in man was similar. A very small percentage of the drug administered was excreted in urine. The pathway of metabolism is not known, but breakdown occurs rapidly and evidence has been obtained suggesting that at least two substances are formed and that one of them may be the active antimalarial agent. Distribution and metabolic alteration are probably the chief factors in controlling the plasma levels. When pamaquin levels were determined in the same person before and after concurrent treatment with even small amounts of quinacrine the maximal plasma values for the former were many times greater when accompanied by the latter and its rate of disappearance was much reduced. This phenomenon of raised pamaquin levels was also observed when a new treatment with pamaquine was begun some months after that with quinacrine had ended. (Quinacrine is known to persist in the body for long periods.) The same phenomenon was not observed to such a degree when quinine or chloroquine was given with pamaquin. The authors consider, however, that sufficient data were not available for definite conclusions to be drawn with the two latter. They believe that localization and metabolism of pamaquin are affected by quinacrine, and that its toxicity is increased. Quinine, on the other hand, increases the antimalarial activity of pamaquin. It has been reported by BLAKE [see below] that these two latter drugs in combination affect haemoglobin metabolism in a manner different from that when they are given alone. *J. D. Fulton*

EARLE, D. P., Jr., BIGELOW, F. S., ZUBROD, C. G. & KANE, Charles A. **Studies on the Chemotherapy of the Human Malarias. IX. Effect of Pamaquine on the Blood Cells of Man.** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 121–9, 1 fig. [13 refs.]

Most of the patients employed in this study were either suffering from malaria or had had the disease from one to six weeks previously. Most were suffering from asymptomatic neurosyphilis, but data were also collected in normal subjects.

Serial methaemoglobin determinations were made in patients receiving various doses of pamaquin, alone or in combination with mepacrine or quinine.

The following table records the maximum methaemoglobin values in patients who had received pamaquin for five or more days, by which time they attain a fairly stable level :—

Treatment group	Number of subjects	Mean per cent. methaemoglobin	Standard deviation	Range per cent. methaemoglobin
Pamaquin, 90 mgm. daily	24	12·2	7·0	0·9–28·7
,, 60 ,, ,,	13	8·9	4·5	1·9–20·8
,, 30 ,, ,,	29	4·4	2·4	0·7–10·0
,, 30 ,, ,, plus mepacrine	6	12·2	4·6	6·0–19·3

The mean methaemoglobin values are proportional to the daily dose of pamaquin except for the small group that received quinacrine in addition : here the values are equal to those recorded in subjects receiving a threefold larger dose of pamaquin. About half the patients in the first three groups were also receiving quinine, an addition that had no influence on methaemoglobin levels.

Acute haemolytic anaemia is the most serious hazard of pamaquin administration. It occurred in seven of 157 patients given pamaquin naphthoate in repeated doses for 2 to 14 days. Six cases occurred among 76 coloured patients, but only one among 81 white subjects.

The administration of 90 mgm. of pamaquin a day for 14 days causes a significant reduction of mature neutrophile granulocytes. This reaction does not occur with daily doses of 30 mgm. unless mepacrine is also administered. The process rapidly disappears when pamaquin administration is stopped.

Norman White

Earle, D. P., Jr., Berliner, R. W., Taggart, J. V., Zubrod, C. G., Welch, W. J., Bigelow, F. S., Kennedy, T. J., Jr. & Shannon, J. A. **Studies on the Chemotherapy of the Human Malarias. X. The Suppressive Antimalarial Effect of Paludrine.** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 130–33. [13 refs.]

The therapeutic trials described were carried out in patients with blood-induced malaria. The infections were the McCoy strain of *P. vivax* (28 patients), the Chesson strain of *P. vivax* which is more resistant than the McCoy strain to quinine, mepacrine and chloroquine (16 patients), and the relatively quinine-resistant Costa strain of *P. falciparum* (9 patients). Paludrine, in varying doses, was administered by mouth. All doses are reported in terms of the free base. The therapeutic results are classified as follows : Class I, no certain effect ; Class II, temporary suppression of parasitaemia or fever or both ; Class III, absence of parasitaemia for 14 days in McCoy *vivax* or 21 days in Chesson *vivax* or Costa *falciparum* infection, followed by a positive reinoculation.

Paludrine was extremely effective against the McCoy strain of *P. vivax*. Total doses of paludrine as low as 50 mgm. produced Class III results with regularity. It was only slightly less effective against the Chesson strain of *P. vivax*. The Costa strain of *P. falciparum* was much more resistant. Total doses of paludrine ranging from 338 to 750 mgm. were given to the nine patients ; Class III effects were obtained in only two.

The conclusion is reached that paludrine is the most active suppressive agent yet described in *vivax* malaria ; it is apparently non-toxic in therapeutic doses.

Norman White

BERLINER, R. W., KENNEDY, T. J., Jr., & BIGELOW, F. S. **A Technique for the Detection of Minimal Numbers of Malaria Parasites ; its Application in the Detection of Suppressed Vivax Malaria.** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 134–7.

A technique is described for the detection of minimal numbers of *P. vivax* parasites in the circulating blood.

Five to 15 ml. of venous blood are drawn into a syringe containing sufficient heparin to prevent clotting. The blood is centrifuged for 20 minutes at 2,000 r.p.m. The plasma layer is carefully removed. The white cells are then aspirated off as completely as possible. The plasma is poured back and gently mixed with the red cells. The reconstituted blood is then carefully layered over an equal volume of bovine albumin solution in a centrifuge tube. (The albumin is prepared by diluting four parts of a 30 per cent. bovine albumin solution with one part of normal saline solution.) The tube is centrifuged for five minutes at 1,000 r.p.m. and then at 2,500 r.p.m. for 15 minutes. The material is now in three layers. The upper layer, the plasma, is discarded. The deepest layer consists of the normal red blood cells that have passed through the middle albumin layer. The latter contains the parasitized red cells which because of their diminished density and the viscosity of the albumin solution have been left behind. The albumin layer is removed and mixed with two or three volumes of isotonic saline in a centrifuge tube and centrifuged at 2,500 r.p.m. for five minutes. The red cells which have been driven to the bottom, where they usually form a layer just sufficient to cover the bottom of the tube, are transferred to a clean slide to form a thick smear which is dried and stained with Giemsa in the usual way.

With this technique the authors were able to confirm the observations made by FAIRLEY [this *Bulletin*, 1945, v. 42, 630] by subinoculations, that the parasites of *P. vivax* first appear in the circulating blood 8½ days after the bite of infected mosquitoes and that the time of appearance is not influenced by suppressive drugs.

Attempts to concentrate parasites in *P. malariae* infections did not succeed ; the parasitized cells are not enlarged. The same is true of cells containing young ring forms of *P. falciparum.* *Norman White*

ROSENFELD, M., ZUBROD, C. G., BLAKE, W. D. & SHANNON, J. A. **Methemalbumin. I. Appearance during Administration of Pamaquine and Quinine.** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 138–43, 6 figs. [18 refs.]

A new compound of albumin and haematin, which does not occur in normal serum, was described by FAIRLEY and BROMFIELD in cases of blackwater fever, and later in cases of severe malaria, nocturnal haemoglobinuria, pernicious anaemia and other conditions, as well as after injection of large amounts of haemoglobin or of haematin. The compound was later named methaemalbumin and its formation and properties described [this *Bulletin*, 1935, v. 32, 828 ; 1942, v. 39, 270, 271]. It had also been observed by other authors in different conditions including pamaquin haemoglobinuria. The reaction between the two components was further investigated by KEILIN [*ibid.*, 1944, v. 41, 1008]. Its appearance was observed consistently by the present authors during combined pamaquin-quinine therapy, but not when either drug was given alone.

Investigations were therefore carried out on four groups of male white volunteer malarial patients infected by mosquitoes with the Chesson strain of *P. vivax*. One group received pamaquin and quinine, a second group pamaquin

alone, a third quinine alone and a fourth pamaquin and quinacrine [atebrin, mepacrine]. Oral treatment was begun on the 5th day of fever, and two days later in the cases receiving pamaquin, being continued over a period of 14 days. Clear unhaemolysed serum was obtained before and after treatment from fasting patients, without the use of an anticoagulant, by centrifuging the blood for ½ hour when drawn. Methaemalbumin shows characteristic absorption and measurements were made in the Beckman spectrophotometer between 300mμ and 650 mμ, with diluted or undiluted serum according to the amount of pigment present. Chemical methods were also used for identification. The most intense absorption band occurs at 405mμ and was used for estimation in the absence of free haemoglobin. Allowance was made for absorption due to bilirubin which was estimated by chemical methods. Methaemalbumin was present in the serum of all patients of the group receiving combined pamaquin and quinine therapy, although in widely different amounts, and continued to increase during the period of treatment. Five days after therapy ended it was no longer present in measurable quantity, and was always absent from the serum of the other three groups. It was formed in the absence of frank haemolysis with which in the past it was most frequently associated. Methaemoglobin was also present in the red cells of patients receiving pamaquin alone or combined with quinacrine and quinine. The causal relationship between these two pigments, if any, is not clear. *J. D. Fulton*

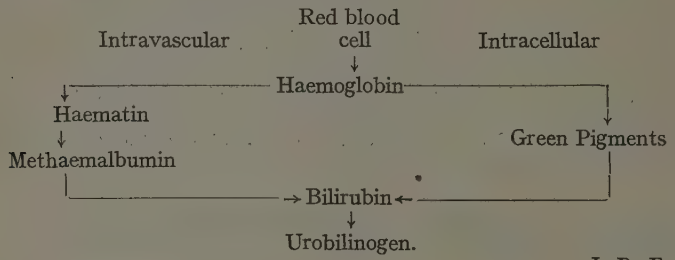
BLAKE, W. D. **Methemalbumin. II. Effect of Pamaquine and Quinine on Pathways of Hemoglobin Metabolism.** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 144–50, 4 figs. [21 refs.]

It has been noted in Part I of this investigation [above] that methaemalbumin occurs during intravascular haemolysis and in a number of other conditions as well as after administration of pamaquin and quinine in combination. The regularity with which the pigment was produced by the two drugs together offered a means of studying its metabolism. The relationship of methaemalbumin production to haemolysis, the effect of drugs on its rate of disappearance as well as the part played by the liver, have been investigated in white patients with syphilis of the central nervous system. Some patients were investigated after malarial therapy when liver function had become normal. Pamaquin and quinine were given orally and their levels in plasma determined at regular intervals to ensure that absorption was taking place. Solutions of haematin and haemoglobin were given intravenously with few untoward results. Estimation of these two substances were made, and also of coproporphyrin, serum bilirubin and faecal urobilinogen.

The increase in amount of the faecal urobilinogen over controls was used as a measure of increased haemoglobin katabolism and occurred during combined therapy with pamaquin and quinine. When haemoglobin was given intravenously in an amount equal to the increased breakdown of this substance caused by combined therapy, no measurable formation of methaemalbumin occurred in normal subjects. It was concluded that haemolysis alone did not give rise to formation of this substance. Intravenous administration of haemoglobin in combination with oral quinine gave rise to the pigment, but when pamaquin replaced quinine only traces of it were formed. A combination of the three substances gave rise to the same degree of methaemalbuminaemia as the combination of quinine with haemoglobin. It seems probable that the drugs in combination cause methaemalbuminaemia by increasing the amount of haemoglobin broken down and also by interference in some way with the pathway of metabolism, the first effect being a synergistic one and the latter due to quinine alone. It emerged that the rate of disappearance of haemoglobin

from serum was not affected by the drugs, but they did appear to slow down the rate of disappearance of the methaemalbumin formed. The effect of pamaquin in delaying conversion of methaemalbumin to bilirubin may be a result of interference with liver function, thus causing the former substance to accumulate on intravenous administration of haemoglobin. Quinine, on the other hand, acts in some way by increasing the degradation of haemoglobin in the vessels to haematin.

Methaemalbumin is regarded as a normal product of haemoglobin metabolism whenever free haemoglobin is present in the serum. Severe haemolysis is necessary before methaemalbuminaemia becomes apparent, unless it is allowed to accumulate in serum as a result of its conversion to bilirubin being slowed down. The accompanying diagram indicates a possible metabolic pathway of intravascular haemoglobin.



J. D. Fulton

DE AZEVEDO, J. F., CAMBOURNAC, F. J. C. & PINTO, M. R. Observações sobre a incidência do sezonismo na Guiné Portuguesa. (Nota preliminar.) [**Observations on the Incidence of Malaria in Portuguese Guinea—a Preliminary Note.**] *An. Inst. Med. Trop.* Lisbon. 1947, Dec., v. 4, 7–15, 1 folding map. English summary.

This note embodies the first results of an investigation initiated in Portuguese Guinea in January and February 1944, as part of the investigations launched by the Mission of the Tropical Medicine Institute of Lisbon. A total of 4,000 thick blood films were examined at first and eventually it was possible to deal with some 10,000.

Detailed regional findings are shown in a lengthy table, and the incidence is shown graphically on a sketch map. *Plasmodium falciparum* was the common species, with *P. malariae* next ; no *P. vivax* were found. Distribution of infection during the dry season was much more irregular than might be expected. There was no correlation between the percentage of persons infected with the particular species of parasite and the distance from the coast of the places where they were found. *H. J. O'D. Burke-Gaffney*

YOELI, M. **Non-Pigmented Malaria Parasites in the Bone Marrow from a Mixed Infection of *Leishmania* and *Plasmodium vivax*.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1948, July, v. 42, No. 1, 99–100, 1 pl.

This paper records the finding, in bone marrow smears, of *Leishmania* parasites accompanied by malaria parasites resembling *Plasmodium vivax* except for the important fact that the latter seemed devoid of pigment. The malaria parasites, asexual and sexual, were all in red cells and, but for the

absence of pigment, had normal morphology. In examination of the peripheral blood before sternal puncture, no malaria parasites were found.

Without examination of the slides, no useful comment can be made.

H. E. Shortt

KETTLE, D. S. **The Growth of *Anopheles sergenti* Theobald (Diptera, Culicidae), with special reference to the Growth of the Anal Papillae in varying Salinities.** *Ann. Trop. Med. & Parasit.* 1948, Apr., v. 42, No. 1, 5–29, 15 figs. [26 refs.]

This is a detailed study of the growth of the larva of *Anopheles sergenti*. Much of the paper is taken up with a statistical analysis of the recorded measurements; this part of the paper it is not possible to summarize, but in general, the object was to discover whether the anal papillae of larvae of anopheline mosquitoes grow during an instar and if so if their growth rate is the same as any other part of the body. In preliminary experiments, second stage larvae of *A. multicolor* were used, when it was observed that the thorax grows in length and breadth throughout the instar but there is no sudden increase at ecdysis. The head breadth remains more or less constant during the instar but shows a relatively enormous increase immediately after ecdysis. The second abdominal segment and the dorsal anal papillae grow steadily in length throughout the whole of the larval life. It is possible therefore to separate the different instars of *A. multicolor* on the head breadth. But this species was rare and as *A. sergenti* was plentiful, the latter was used for this investigation.

Five hundred larvae were used, 125 in each instar. Seven measurements were made on each larva: length and breadth of head, thorax and second abdominal segment and the length of the dorsal anal papillae. The larvae in each instar were divided into six classes based on the size of the thorax breadth. In diluted sea-water (equivalent to a 0·25 per cent. solution of NaCl) the thorax and second abdominal segment grew steadily, the head grew hardly at all during each instar but increased enormously at each ecdysis, while the anal papillae lengthened during the instar and increased suddenly at ecdysis.

The growth of the dorsal anal papillae was further investigated in larvae reared in various dilutions of sea-water. The eggs from several females were mixed and then divided into eight batches which were reared under similar conditions other than the salinity of the water. Fourth-stage larvae having a thorax breadth of 1,000μ were taken as standard, and of those kept in distilled water the papillae were very long (313μ), in tap water they were smaller (210μ) and in sea-water (equivalent to 0·1 per cent. NaCl) they were 190μ. There was no change as salinity increased to 0·75 per cent. NaCl but in 1·0 per cent. and 1·1 per cent. they were distinctly shorter (152μ).

The author discusses various suggestions which have been put forward to account for this variation in the lengths of the anal papillae of larvae reared in different salinities and concludes that while the enlargement in distilled water "is regarded as a functional hypertrophy connected with the uptake of chloride ions", the nature of the mechanism which regulates the length of the papillae is unknown. Whatever it may be, he suggests it is the same as that which controls the chloride content of the haemolymph.

H. S. Leeson

FAIN, A. & HENRARD, C. Quelques moustiques du fleuve Congo (Chenal) et des rivières Kasai et Kwango. [**Some Mosquitoes of the Congo, Kasai and Kwango Rivers.**] *Ann. Soc. Belge de Méd. Trop.* 1948, Mar. 31, v. 28, No. 1, 7–20. [11 refs.]

A list is given of the mosquitoes collected in African huts and European houses in villages along the Congo River from Léopoldville north to Kwamouth,

east along the Kasai to Banningville and south along the Kwango for about 80 kilometres. Altogether, nine anophelines and twenty-six culicines are recorded. Generally speaking, in the riverine villages *Anopheles moucheti* was predominant, which may have been due to the time of collecting, after 7 p.m. Small numbers of *A. gambiae* were occasionally taken, but along the Kasai river *A. wellcomei* became so abundant that at Wissman Pool it outnumbered *A. moucheti*. *A. funestus* was taken once at one village in the interior, where, however, *A. paludis* was the common species. *H. S. Leeson*

LEWIS, D. J. **The Mosquitos of the Jebel Auliya Reservoir on the White Nile.** *Bull. Entom. Res.* 1948, May, v. 39, Pt. 1, 133–57, 1 map, 6 figs. on 1 pl. & 3 text figs. [30 refs.]

The Jebel Auliya Reservoir is situated in the Sudan and extends some 530 kilometres up the White Nile from the dam of the same name. This area comprises the reservoir, thousands of acres of seasonal swamps, irrigated areas and rain-water pools. The author discusses the topography, climate, population, vegetation, predaceous insects and fish and the effect of the dam on the breeding places of mosquitoes, of which forty-three forms have been found in the area.

Collections of mosquitoes were made during several visits to the reservoir between 1937 and 1946. Some results of collecting under various conditions in the Kawa section (the middle third) are summarized in four tables. Malaria occurs throughout the area and appears to have increased since the dam was constructed.

Anopheles gambiae is probably the main vector of malaria, and its breeding places, which are comparatively small and well defined, can be treated with DDT in oil or with Paris green. *A. rufipes* is provisionally regarded as a vector, though of less importance than *A. gambiae*; its control would be a considerable problem as its breeding places are more extensive. Pyrethrum spray is used in houses against this species, and parts of swamps are treated with Paris green dust or DDT in oil. *A. pharoensis* is present in millions though of little importance as a malaria vector. The treatment against larvae is similar to that of *A. rufipes*. *A. funestus* occurs in the south, in the Jebelein section, though its northern limit is some miles further north in the Kawa section. Intensive house spraying appears to be the feasible method of control in the few villages that exist.

Paris green dust seems to be the ideal larvicide in this area, because as it drifts with the wind its application does not necessitate wading in channels which may be infected with schistosome cercariae. An improved Paris green mixer is described and illustrated. *H. S. Leeson*

See also p. 1037, ABBOTT, **The Culicidae (Diptera) of Darfur Province, Anglo-Egyptian Sudan, with Observations on the Geography and Zoogeographical Relations of the Region.**

MARA, L. Studio morfologico dell'uovo di "*Anopheles dancalicus*". (Corr. 1939). [**Morphology of** *Anopheles dancalicus*.] *Boll. Soc. Ital. di Med. e Igiene Trop.* (Sez. Eritrea). 1948, v. 8, Nos. 1/2, 76–83, 4 figs. [11 refs.] English summary.

ROBERTS, F. H. S. & O'SULLIVAN, P. J. **Studies on the Behaviour of Adult Australasian Anophelines.** *Bull. Entom. Res.* 1948, May, v. 39, Pt. 1, 159–78, 2 graphs & 1 fig. [10 refs.]

Observations were made on adult anopheline mosquitoes at Cairns, North Queensland from January to April, 1944; at Salamaua, New Guinea from

May to July; and at Mirivasi, New Guinea from August to October. The species studied were *Anopheles punctulatus punctulatus*, *A. p. farauti* and intermediate forms, and *A. amictus hilli*. The authors record in detail their investigations into prevalence and activity, by day and by night; biting habits; daytime haunts; host preferences and methods of determination of the age of female mosquitoes by condition of the wings, ovarian development and state of digestion.

All forms of *A. punctulatus* have much in common, though behaviour may differ slightly according to local conditions. Adults usually disperse from breeding places and congregate around the source of the blood meal; for example, human settlements. Greatest activity commences after dark but no marked periodicity was observed at dawn and dusk, as has been widely held. They do not indulge in long continuous flights but females have been found a mile from breeding places and males 600 yards away. After feeding, the females rest in the huts a short time, then fly out; their outdoor resting places are among vegetation near the ground; other females and males also are there and fertilization is assumed to take place here, not at the breeding place; males do not normally enter houses but stay in the bush. Pyrethrum sprays in huts in the daytime have therefore little effect, but the application of DDT to the walls is more promising. Precipitin tests showed that *A. p. farauti* has no pronounced preference for either animal or human blood but in *A. p. punctulatus* anthropophilism was marked. All forms seemed more attracted to the indigenous people in Salamaua than to the white man.

The behaviour of *A. amictus hilli* is similar in most respects to that of the *punctulatus* forms. One difference was, however, noted: *A. a. hilli* gathers in large numbers around the breeding places, where the males remain, and fertilization probably takes place here and not in the bush. The daytime resting places of females awaiting a meal were not determined and the host preferences were not fully explored by the precipitin test, but this anopheline is known to be a vicious pest in Northern Queensland.

Very little is known of the habits of other anophelines. *A. bancrofti bancrofti* rarely attacks man at Cairns, but in the Northern Territory has been reported to have an infection rate of 4·3 per cent. *A. annulipes* is an extremely common species, well distributed throughout Australia and extending into New Guinea It is probably a malaria vector in sporadic cases outside the *farauti* area. [See also this *Bulletin*, 1945, v. 42, 1049; 1947, v. 44, 275.] *H. S. Leeson*

ROZEBOOM, L. Transmisión de la malaria en el Nuevo Mundo. [**Transmission of Malaria in the New World.**] *Medicina*. Mexico. 1948, Feb. 25 & Mar. 10, v. 28, Nos. 550 & 551, 85–93; 100–112.

BASHAM, Ernestine H. & HAEGER, J. S. **Records of** *Anopheles quadrimaculatus* **Say for the Florida Keys.** *Mosquito News*. 1948, June, v. 8, No. 2, 72.

PEFFLY, R. L., DAVIDSON, R. H. & WATERS, H. A. **Studies in Laboratory Rearing of** *Anopheles quadrimaculatus* **Say.** *Ohio J. Sci.* 1946, v. 46, No. 2, 65–70, 2 figs.

COUTINHO, J. DE O. Contribuição para o estudo da distribuição geográfica dos anofelinos do Brasil. Sua importância na transmissão da malária. [**Geographical Study of Anophelines in Brazil and their Importance in Transmission of Malaria.**] [Thesis.] Universidade de São Paulo, Faculdade de Medicina. 1947, Dec., 117 pp., 2 maps. [Bibliography.]

According to the present author there are in Brazil 48 species of *Anopheles*, and 3 of the related genus *Chagasia*. A table gives the distribution of the *Anopheles* in the separate states of Brazil.

The bulk of the paper takes separate states and in each shows the local distribution of the species of *Anopheles* which occur, the proportion of adults found in houses and so forth. The thesis contains a wealth of local detail.

In Brazil, *Plasmodium* has been found in six species of *Anopheles*. The salivary gland rate was 1·55 per cent. of 579 *A. darlingi*: the rate was between 0·35 and 0·20 per cent. in considerable numbers of *A. tarsimaculatus, cruzii, bellator* and *homunculus*; it was 0·02 per cent. in 3,938 *A. albitarsis*.

P. A. Buxton

LAMPEN, H. Inducierte Malaria nach Bluttransfusion. [**Malaria transmitted by Blood Transfusion.**] *Med. Klin.* 1947, May, v. 42, No. 9, 371–2.

Owing to the risk of disease being transmitted by blood transfusion a law was passed in Germany in March, 1940, that donors must be free from tuberculosis, skin disease, venereal or tropical diseases. In spite of every care this freedom from infection cannot always be guaranteed. The author quotes the case of a man who, in May 1943, was given a transfusion of 450 cc. of blood on account of anaemia produced by peptic ulcer. Great pains had been taken to eliminate risk of the diseases mentioned, but just a month later, on the 7th, 9th, 12th and 14th days of June, the patient had attacks of fever and shivering, and examination revealed tertian malaria parasites in his blood. The donor had not had a day's illness for more than 20 years, but a history was obtained (although no parasites could be seen in two examinations of his blood) that in 1915, or 28 years before, he had been a prisoner of war in Southern Russia and had there suffered from malaria, tertian type, but, though he had occasional attacks for 5 years afterwards, he had been quite free from them since 1920, that is 23 years before his blood was used for transfusion. All other sources seemed to be excluded.

H. Harold Scott

ARU, L. La ricerca del parassita malarico mediante arricchimento. (Nota di tecnica.) [**Enrichment Method for finding Malaria Parasites.**] *Riv. di Malariologia.* 1948, Feb., v. 27, No. 1, 47–52, 3 figs. English summary.

After brief reference to methods of detection of malaria parasites, by special staining, by thick drop and enrichment methods, the author describes the one used at the Institute of Hygiene and Bacteriology of the University of Cagliari and Sardinia. Five cc. of blood are taken from a vein into citrate and centrifuged at a low speed for 15 minutes; with a capillary pipette are drawn off, first the serum [? plasma], then the layer of leucocytes and the platelets which lie above the red corpuscles. Care is needed because, if many white cells are left the resulting preparation is confused. The parasites are fixed by 10 per cent. formol for 20 minutes and the red cells haemolysed in 20–30 cc. of 0·35 per cent. NaCl for 10–15 minutes. The whole is then centrifuged for 5 minutes; the supernatant fluid is removed, leaving two or three drops for emulsifying the deposit. Preparations are spread from this, dried in the thermostat or at room temperature, and stained with Giemsa's stain, 10 per cent. The author claims that this procedure gives a permanent preparation and a concentration of 50–150 times the original.

H. Harold Scott

v. HALLER, E. Ueber die Ursache und das Auftreten von Rückfallen bei der Malaria tertiana. [**An Examination of the Origin of Relapses in *P. vivax* Malaria.**] *Med. Klin.* 1947, May, v. 42, No. 10, 417–21, 2 charts.

The essence of this paper is to be found in the theoretical considerations which have convinced the author that in benign tertian malaria an EE, or tissue cycle, which he presumes to be in the endothelial cells of the capillaries, must take

place. The reasoning which has led him to these conclusions is now well understood, but he is, of course, ignorant of the recent classical demonstrations by SHORTT and GARNHAM. A detailed review of this communication has now lost its chief point, though it is interesting to observe how near to the real truth his arguments are. He observes, for instance, how in the Sardinia-infected military cases relapses of *P. vivax* were extremely uncommon, whilst in a prisoner-of-war hospital on the Adriatic coast nearby they were invariably the rule. This anomaly he would explain by the disparity in the primary dose of sporozoites. On the persistence of the EE cycle the spring and autumn relapses of primary infections can also best be explained. In this manner the existence of climatic or other provocative factors is discounted. He asserts too that the timing of relapses is due to the presence or absence of immune bodies in the blood stream, which destroy the merozoites on liberation from the tissue stages—another prophecy which bids fair to come true, and he suggests that these immune substances can exert no action on the EE forms. In this respect the reaction is the same whether the primary infection is slight or severe. Any therapeutic measures which are directed towards the extirpation of the erythrocytic stages cannot prevent relapses from occurring at their predestined intervals, so that the only reasonable therapy is one directed towards the destruction of the tissue stages of the parasite. The absence of any provocative factors cannot be regarded as of any prognostic significance.

All these arguments now resound with a genuine ring.

P. Manson-Bahr

LOMBARD, Frances F. **Review of Literature on Cinchona Diseases, Injuries, and Fungi.** *U.S. Dept. of Agric. Bibliographical Bull. No.* 9. Wash. 1947, Dec., 70 pp. [290 refs.] Superintendent of Documents, U.S. Govt. Printing Office. [20 cents.]

WINCKEL, C. W. F. De vermindering der recidieven van malaria-aanvallen door behandeling met kinine en plasmochine. [**The Reduction of Malarial Relapses with Quinine and Plasmoquine.**] *Nederl. Tijdschr. v. Geneesk,* 1948, Aug. 14, v. 92 (iii), No. 33, 2507–16. [Refs. in footnotes.]

A general review.

MAIER, J. **The Absorption of Quinine and Quinacrine in Dysentery Patients.** *Amer. J. Trop. Med.* 1948, May, v. 28, No. 3, 397–400.

During the recent war American troops in New Guinea frequently suffered from malaria and dysentery at the same time, in spite of the fact that quinacrine (mepacrine) in 0·1 gm. daily doses was supposed to be taken as a routine. It seemed possible that in these circumstances the drug was not being absorbed. Investigations were therefore carried out on patients with severe or moderately severe dysentery to determine whether oral quinacrine or quinine was normally absorbed or whether some other form of administration was necessary. The patients were divided into three groups and received treatment according to the following dosage schedules. Group 1, consisting of 14 patients, were given 40 grains of quinine daily as well as intensive sulphaguanidine treatment; non-dysentery patients were used as controls and received the same drug treatment. A similar number of patients in Group II received intensive sulphaguanidine treatment along with 3 doses of 0·3 gm. quinacrine on the first day and 3 of 0·2 on the second day. Plasma levels of both drugs were determined by the method of BRODIE & UDENFRIEND [this *Bulletin*, 1944, v. 41, 453]. The 19 patients in Group III were given 3 doses of 0·3 gm. quinacrine only on the day of admission and the plasma drug level was measured. Quinacrine plasma

levels were also measured in two patients without dysentery, but who were also receiving sulphaguanidine. This substance did not interfere with quinacrine estimations.

There was no relationship between the severity of diarrhoea and the plasma levels of the drugs. It was concluded that the drugs were absorbed in the normal way when given by mouth to patients with diarrhoea as the result of acute bacillary or non-specific infection. *J. D. Fulton*

KAHLSTORF, A. Ueber eine Leberschädigung durch hohe Atebrindosen. [**Damage to the Liver from Large Doses of Atebrin.**] *Klin. Woch.* 1947, July 15, v. 24/25, Nos. 39/40, 632–3.

Considering how widespread has been the use of atebrin [mepacrine] in malarial conditions, reports of untoward by-effects have been surprisingly few. Except for gastro-intestinal disturbances, on the whole mild in degree, the chief have been mental or psychic—a sense of fatigue and depression leading perhaps to thoughts of suicide.

In the present contribution the author records the case of a young soldier, 21 years of age, hitherto enjoying the best of health. He gave a history of having taken in 3 weeks 70 "small tablets" of atebrin and in the following week 10 "large tablets"—at least 5·2 gm. altogether (probably more). He became jaundiced and was admitted to hospital. The upper part of the abdomen was tender to pressure but the liver was not, at that time, enlarged. During the ensuing fortnight the jaundice increased. The urine gave a strongly positive acridine reaction, the Takata-Ara reaction of the serum was marked and the liver was enlarged and could now be felt three fingers' breadths below the costal margin; there was increased excretion of galactose in the urine after 50 gm. were taken—in successive hours, 1 gm., 1·23 gm. and 0·25 gm., or 2·48 gm. altogether.

The hepatic condition, it was concluded, was due to the atebrin taken. Further investigations are to be undertaken to determine the pathogenesis of the action of the drug and whether the damage to the parenchyma is due to its action on the liver capillaries. *H. Harold Scott*

WALLS, E. S. **Paludrine.** [Correspondence.] *Brit. Med. J.* 1948, July 24, 225–6.

Walls writes from Sierra Leone. He has not found that paludrine in doses of 0·1 gm. twice a week can be relied upon to prevent attacks of malaria in himself or his patients, but in doses of 0·1 gm. each day it is about equal to quinine and mepacrine in its suppressive effects and has the advantage that it is not toxic and does not stain the skin. For treatment he gives 0·1 gm. three times each day for 10 days, and on the first day he also gives two doses of quinine (10 grains each).

In general, he prefers paludrine to the other drugs, but in doses greater than those hitherto recommended by the makers. *Charles Wilcocks*

ROBERTSON, J. D. **Paludrine Treatment of School Children.** *Zanzibar Med. & San. Rep. for Year ended 31st December, 1947.* Appendix II, 24–5.

This investigation is reported by Dr. J. D. Robertson, Pathologist, Zanzibar.

About 50 children in each of three schools [presumably African pupils] were given 0·1 gm. paludrine on two days a week from September, 1947. In addition, the children at one school were given iron and cod liver oil on the remaining days. A fourth group of pupils from one of the schools received no paludrine or

other medication and served as a control. The children were examined for spleen and parasite rates before treatment and again in 6 weeks and 3 months.

The parasite rate, which averaged 50 per cent. initially, fell to nil in the treated children in 6 weeks, and although it "tended to fall naturally" the controls still showed a rate of 26·8 per cent. after 3 months.

Splenic enlargement fell from 60 per cent. to 18 per cent. over the period of treatment, but remained at 56 per cent. in the untreated controls.

The haemoglobin levels were unchanged in all groups and the iron supplement caused no improvement.

The figures for the rates in each group are shown in three tables: the author concludes that the dosage of paludrine, 0·1 gm. twice weekly, was a little too small to be completely effective. *H. J. O'D. Burke-Gaffney*

ANSARI, M. Y. **Anti-Malarial Drugs Old and New, with some Observations on Paludrine in Malaria.** *Indian Physician.* 1948, July, v. 7, No. 7, 177–84.

This paper is largely a review of the relative efficacy of the different anti-malarial drugs; but it contains a personal observation by the author on the use of paludrine in the treatment of about 20 patients suffering from benign tertian and malignant malaria [further details of the cases are not given].

The drug was used in dosages ranging from 50 mgm. to 300 mgm. daily, and was administered as (1) a single initial dose of 300 mgm. and then 100 mgm. weekly for 6 weeks, (2) twice daily doses of 100 mgm. for 14 days, (3) 25 mgm. twice daily for 14 days; this was tried in one case only and was found to be as effective as (2) above.

It is stated that "with the dosage mentioned above and the method used", temperatures became normal in 1 to 3 days and parasitaemia disappeared in 2 to 4 days. There were no relapses during the patients' stay in hospital (7 to 35 days). No toxic effects were noted with these dosages. Gametocytes were unaffected. *H. J. O'D. Burke-Gaffney*

MAEGRAITH, B. G. **Paludrine in the Treatment and Control of Malaria.** *An. Inst. Med. Trop.* Lisbon. 1947, Dec., v. 4, 413–26, 2 folding figs. [14 refs.]

A lecture given at the Institute of Tropical Medicine, Lisbon.

FITZHUGH, O. G., NELSON, A. A. & HOLLAND, Oma L. **The Chronic Oral Toxicity of Chloroquine.** *J. Pharm. & Exper. Therap.* 1948, June, v. 93, No. 2, 147–52, 1 chart.

Chloroquine (SN 7618), which is 7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline, was synthesized during the last war in America and proved an active antimalarial agent. A report on its properties was made by LOEB [this *Bulletin*, 1946, v. 43, 708] and WISELOGLE [Survey of Anti-malarial Drugs, 1941–1945, *ibid.*, 1947, v. 44, 1106]. According to MOST *et al.* [*ibid.*, 1946, v. 43, 1011] it appeared to be more active than quinine and quinacrine (atebrin, mepacrine) in *P. vivax* infections under the conditions of test. The present report in which experiments lasted 2 years compares the earlier results of the authors [*ibid.*, 1946, v. 43, 525] on the chronic oral toxicity of quinacrine with those obtained with the newer drug.

Groups of 10 male and 10 female rats 21 days old were given six diets containing from 100 to 1,000 p.p.m. chloroquine, to which they had free access in individual cages under controlled conditions of temperature and humidity.

The growth of rats on the diet with 100 and 200 p.p.m. did not differ from controls. With 400 p.p.m. there was early retardation of growth, but at the end of one year the variation from controls was not significant. Higher doses reduced growth and caused death within a year. Leucocytosis, chiefly neutrophilic, resulted from continued administration of medium or high doses; haemoglobin and red cell numbers were also increased by the latter.

The principal lesions encountered were a focal necrosis of striated muscle, especially cardiac, and necrosis and fibrosis of the central lobules of the liver. There was a marked distinction in frequence and severity of the lesions between 400 and 800 p.p.m. dose levels. At 200 p.p.m. or below lesions were slight. From calculation it appeared that the dosage of chloroquine which would produce toxic effects in rats is higher than either the therapeutic or prophylactic dosage recommended for man. The general inference of the authors was that chloroquine is slightly less toxic than quinacrine for rats. The pathological lesions caused by these drugs showed similarities. *J. D. Fulton*

STRAUS, B. & GENNIS, J. **Evaluation of Pentaquine as a Cure of Relapsing Vivax Malaria. A Controlled Study of Ninety-Five Cases.** *Bull. New York Acad. Med.* 1948, June, v. 24, No. 6, 395–6.

This study was designed to test the efficacy of pentaquine combined with quinine in the therapy of naturally acquired *P. vivax* infections in man. The patients were ex-servicemen in the Veterans' Administration Hospital, Bronx, New York, and totalled 95; 84 of them had served in the south-west Pacific theatre. All had *P. vivax* infections. Controls were made with chloroquine (SN 7618) because it is highly effective in treatment of the attack but has little, if any, effect on relapses. It was given as the diphosphate in a dosage of 0·6 gm. of base followed in six hours by 0·3 gm. and 0·3 gm. on the 2nd and 3rd days. Pentaquine was given as the monophosphate in a daily dose of 30 mgm. base (10 mgm. every 8 hours) with 0·6 gm. of quinine sulphate for 14 days. The dosage of pentaquine is half the recommended daily dose of 60 mgm. of base. This reduced dose was used to decrease toxicity and was regarded as feasible as it was likely that most of the men would have had some degree of immunity.

The study began in January 1947, with 46 patients in the chloroquine group and 49 in the pentaquine-quinine group. Follow up, which varies from 1 week to 14 months, will continue for at least a year. At present 85 per cent. of patients have been followed up for more than 4 months. To date, none of the patients in the pentaquine group has relapsed; 14 of the chloroquine group have relapsed (12 from the S.W. Pacific). One patient had three relapses and two had two relapses.

Toxic manifestations in the pentaquine-quinine group were mostly insignificant, though some did occur in 75 per cent. of patients. In no case was it necessary to discontinue pentaquine, though quinine had to be discontinued in one case. Nausea, anorexia and occasionally vomiting occurred commonly in the first 4 days and mild abdominal pain after the first week. Tinnitus, dizziness and headache were not uncommon. Six patients showed a decrease of 1 million red blood cells or less per cmm., but no frank haemolytic reactions were seen. Fever (99·6°–103·4°F.) lasting for one day occurred in 7 patients from the 7th to the 11th day. It is suggested that many of the toxic manifestations were probably due to quinine.

The results so far suggest that one-half of the previously recommended dosage of pentaquine eradicates relapsing *vivax* malaria.

H. J. O'D. Burke-Gaffney

WRIGHT, C. I. & SABINE, Jean C., with technical assistance of Anne H. WRIGHT. **Cholinesterases of Human Erythrocytes and Plasma and their Inhibition by Antimalarial Drugs.** *J. Pharm. & Exper. Therap.* 1948, June, v. 93, No. 2, 230–39, 5 figs. [20 refs.]

The study now reported forms part of a wider investigation undertaken to find if any relationship exists between antimalarial activity and toxicity of chemical compounds and their inhibitory action on cholinesterase. The enzyme present in red cells and plasma was used, as qualitative differences have been ascribed to them. The antimalarial drugs employed were quinine, quinidine, plasmoquine, quinacrine [atebrin, mepacrine], chloroquine and paludrine. Their inhibitory power was estimated manometrically by their effect on hydrolysis of acetylcholine. Suitable dilutions of the enzyme preparations were in the reaction flask and acetylcholine was added from the sidearm. Chloroquine and quinacrine inhibited the enzymes from both sources about equally, while the remaining four drugs were less effective against that from red cells. There was no correlation between inhibitory action on cholinesterase and antimalarial activity or toxicity. *J. D. Fulton*

MACDONALD, G. **The Policy of Malaria Prevention.** *An. Inst. Med. Trop.* Lisbon. 1947, Dec., v. 4, 373–90. [12 refs.]

A lecture given at the Institute of Tropical Medicine, Lisbon.

MACDONALD, G. **The Place of DDT as an Anopheline Larvicide.** *An. Inst. Med. Trop.* Lisbon. 1947, Dec., v. 4, 391–411, 5 figs. (2 on 1 pl.) [18 refs.]

A lecture given at the Institute of Tropical Medicine, Lisbon.

WATERHOUSE, D. F.; ATHERTON, D. O. **Spray Tests against Adult Mosquitoes. 1. Laboratory Spray Tests with Culicine** (*Culex fatigans*) **Adults** [WATERHOUSE]. *Commonwealth of Australia. Council for Sci. & Indust. Res. Bull. No. 219*, pp. 1–27, 3 figs. [11 refs.] **2. Spray Tests with Anopheline** (*Anopheles punctulatus farauti*) **Adults** [WATERHOUSE & ATHERTON]. *Ibid.*, pp. 29–40, 2 pls.

1. The first paper deals with initial exploratory tests of sprays against *Culex fatigans* under standardized laboratory conditions in Canberra, during 1942 and 1943. They were designed to provide information on the minimum effective concentration of pyrethrins and also to evaluate the effectiveness of Lethane, Thanite, DDT and other synthetic materials.

Eggs of *C. fatigans* were collected in the field and reared to adult stage in the laboratory at 80±1°F. (26 to 27°C.) and 70±2 per cent. relative humidity. The adults were kept in cages for four to six days after emergence and fed on fruit, not blood. The tests were made in a Peet-Grady chamber with the standard spray gun and a 2 ml. dosage (one-sixth of the standard dose for flies) equivalent to 1 fl. oz. per 3,000 cu. ft. The spray was applied at 12·5 lb. air pressure and the mosquitoes remained exposed to the mist for ten minutes. They were then all collected and after the percentage knockdown was calculated, were transferred to a clean cage with fresh apple and left for twenty-four hours. At the end of this time the percentage mortality was recorded.

About 350 tests were made on more than 30,000 mosquitoes. The results show that a spray of 0·14 per cent. pyrethrins gave 99·3 per cent. knockdown and kill. DDT and Thanite also showed promise. A spray containing 1·0 per cent. DDT gave 94 per cent. mortality but only 55 per cent. knockdown; the addition of 0·1 per cent. DDT to a 0·01 per cent. pyrethrins spray increased mortality by 16 per cent. A 3·5 per cent. Thanite spray was about equal in

effectiveness to the 0·14 per cent. pyrethrins spray, but 2·5 per cent. Thanite added to a 0·01 per cent. pyrethrins spray resulted in a lowering of both knock-down and mortality. Lethane was neither highly toxic to the mosquitoes nor did it serve any useful purpose when added to a pyrethrum spray. Other synergists had little or no effect on pyrethrum sprays used against *C. fatigans*.

2. The second series of tests was an extension of the laboratory experiments recorded in the first paper. They were made in tents or native huts with caged wild-caught females of *Anopheles punctulatus farauti*, at Lalapipi in New Guinea in September, 1943. Dosages of 1 fl. oz. per 2,100 cu. ft. and 1 fl. oz per 3,000 cu. ft. were atomized by pressure sprayer and by hand spray gun. An exposure of ten minutes was allowed and the percentage knockdown noted. The tent was aired for twenty minutes and mortality rates were recorded after 1, 5 and 18–20 hours. Temperature varied between 82 and 90°F. (27·5 and 32°C.) and relative humidity between 68 and 92 per cent. A total of 10,866 female mosquitoes were used in 236 experiments in which 32 sprays were tested.

The results agree (except for Thanite sprays) with the laboratory tests on *C. fatigans* described in the first paper. The reason was probably the greater fumigating effect in the Peet-Grady chamber.

For sprays containing pyrethrins alone it would not be desirable to use solutions weaker than 0·07 per cent. pyrethrins which gave 99·5 per cent. knockdown and 99 per cent. kill (concentrations above this gave complete kill and knockdown). A 0·5 per cent. DDT spray gave 97 per cent. mortality but only 33 per cent. knockdown; however, the addition of 0·03 per cent. pyrethrins improved the knockdown to 98 per cent. Five per cent. Thanite + 0·5 per cent. DDT mixture gave good knockdown and high mortality. The use of such an unpleasant spray would only be justified if pyrethrins were not available.

In practice these sprays gave freedom from attack by *A. p. farauti* for about five minutes and they had no persistent lethal effect, but the application, in one tent, of DDT at the rate of 50 mgm. per sq. ft. freed it of resting anophelines for some weeks.

The evidence provided by the tests in the second paper confirmed the decision of the Australian Army authorities not to vary the 0·14 per cent. pyrethrins spray, adopted provisionally as a result of the tests reported in the previous paper, and not to include a synergist. This was used until the advent of DDT, in the last year of the war, in sufficient quantity to reinforce the spray and convert it into an all-purpose one. *H. S. Leeson*

BRITISH GUIANA. **Report of the Honorary Government Malariologist for the Year 1947** [GIGLIOLI, G.]. **Mosquito Control Operations by Residual D.D.T. in British Guiana. Filariasis Survey of the Coastlands.** 14 mimeographed pp., 1 map.

In January 1947, the Yellow Fever Service and the Malaria Research Unit of British Guiana were combined into a Mosquito Control Service. The DDT residual spraying of houses was made compulsory in localities declared as DDT control areas by the Director of Medical Supplies.

Meteorological and population figures are listed and the organization of spraying units is described. Malaria is either endemic or hyperendemic in the coastlands, estuaries and in suburbs and peripheries of towns. In the interior it is widespread and hyperendemic in most communities. The vector is *Anopheles darlingi*. *A. aquasalis* and *A. albitarsis* were not proved to be transmitters of malaria, but they are potential vectors and possibly maintain a small proportion of local malaria, *e.g.*, in the north-west, where *A. aquasalis* appears to be a carrier. These species, with *A. triannulatus*, are zoophilic and non-domestic and are thus not affected by DDT house-spraying.

The aim is to treat all buildings in control areas with 150 mgm. DDT per square foot at intervals of eight months, which may later be extended to 10 or even 12 months. In 1947, 32,458 buildings in the coastal area were treated, involving 262,832 persons or 89 per cent. of the coastal population and 70 per cent. of the total population. Spraying in the remaining parts is now proceeding. In the interior, considerable spraying was done by the mining companies.

Immediately after treatment, adults of *A. darlingi* disappear and larvae disappear two or three weeks later. It is claimed that in these areas *A. darlingi* has now been eradicated. Figures are given to show the reduction in spleen rates and the slower reduction in the parasite rates.

A survey of filariasis is proceeding and figures are given for 1946–47 showing the distribution by race, sex and age and the degree of infestation, etc. It is expected that the effect of the DDT sprayings on the incidence of filariasis will be much slower in its development than it is on the incidence of malaria.

A monograph on mosquito-borne diseases in British Guiana and on three years of investigation on their control by DDT is being prepared and will soon be available.

The report concludes with a list of publications issued during the year.

H. S. Leeson

PRATT, H. D. **Relation of Plants to Malaria Control in Puerto Rico.** *Supplement No. 200 to Pub. Health Rep.* Wash. 1947, Dec., 38 pp., 3 charts & 10 figs. [11 refs.]

This paper describes plant communities in Porto Rico and their relations to anopheline production. Various plant associations are described and control methods appropriate to them.

Examples are, the control of *A. albimanus*, breeding in mangrove swamps by drainage, dusting and "salting up" from sea-level canals; and the drainage of flats and oiling of temporary pools where *Batis maritima* and *Sesuvium portulacastrum* dominate and lead to the breeding of *Aëdes taeniorhynchus*, *Aëdes sollicitans* and *Psorophora confinnis* and *P. pygmaea*. In coastal swamps where *Typha angustifolia* and *Phragmites* dominate, *albimanus* breeds only at the sunlit margins, and drainage and dusting with Paris green has been successful. For grasslands and pasture, where temporary pools in small depressions or in hoofmarks may lead to heavy breeding the plant associations are dealt with in some detail. It is pointed out that tall grasses may render larvicidal methods difficult, and control by drainage is recommended. Sugar-cane fields present a special problem. In newly cut fields there is little breeding, but as the trash sinks into the irrigation ditches and the water surface becomes sunlit, and especially when the ditches are reflooded after fresh planting, then *A. albimanus* increases, until after the canes reach a metre in height, when *A. grabhamii* gradually replaces *albimanus*. When the canes are at full height, *A. vestitipennis* may be the only species present.

Plants which tend to inhibit anopheles production are listed, such as duckweed, *Azolla*, *Pistia* and other species which make floating mats. *Ceratophyllum demersum*, on the other hand, produces mats beneath the surface and so protects anopheles larvae from natural enemies; and, in Porto Rico this species is particularly associated with *albimanus*. Other plants of similar habit (*Chara*, *Utricularia*) have the same effect.

The use of the cable saw for clearing subaquatic vegetation, plants useful in bank sodding, and the methods used for eliminating *albimanus* breeding in flotage in sheltered water behind sandbars are also described. Finally, a key, based on simple vegetation characteristics, to the 138 important plant species associated with anopheles in Porto Rico is given.

C. G. Johnson

GILROY, A. B. **Malaria Control by Coastal Swamp Drainage in West Africa.**
This book is reviewed on p. 1043.

SANDOSHAM, A. A. **Malaria in Malai. A Handbook for Anti-Malaria Students.**
This book is reviewed on p. 1045.

RODHAIN, J. Contribution à l'étude des Plasmodiums des anthropoïdes africains. Transmission du *Plasmodium malariae* de l'homme au chimpanzé. [**Transmission of Human** *Plasmodium malariae* **to the Chimpanzee.**] *Ann. Soc. Belge de Méd. Trop.* 1948, Mar. 31, v. 28, No. 1, 39–49.

The author had previously shown that the quartan malaria parasite (*P. rodhaini*) of chimpanzees was transmissible to man [this *Bulletin*, 1943, v. 40, 438] giving rise to an infection indistinguishable from that caused by *P. malariae*. He now reports the results of the inoculation of human *P. malariae* into chimpanzees. The first attempts were negative, but in 1947 three transmissions of a strain obtained from Mr. P. G. Shute of Horton were successful: 10–15 cc. of defibrinated blood containing numerous *P. malariae* parasites were inoculated intravenously into young chimpanzees. The parasites were subsequently found for varying periods in the peripheral blood, augmenting to a crisis when as many as 7,000 per cmm. were found in one case. The animals showed no ill-effects from the disease. The infection disappeared spontaneously in one of the chimpanzees, but still continued in a very sparse form in the remaining two. Blood from one chimpanzee at the height of the infection was put back into a human being and gave rise to a typical attack of quartan malaria. The chimpanzee must therefore be regarded as a reservoir of *P. malariae* in Central Africa.

[It is now more than ever certain as a result of these experiments that *P. rodhaini* should be regarded as being a synonym of *P. malariae*.]

P. C. C. Garnham

RIGDON, R. H. **A Consideration of the Use of Blood and Oxygen as Supportive Therapy in the Treatment of Malaria.** *Amer. J. Clin. Path.* 1948, June, v. 18, No. 6, 485–90, 3 figs. [11 refs.]

In various publications since 1941 [this *Bulletin*, 1943, v. 40, 118, 436; 1946, v. 43, 309, 630; 1947, v. 44, 505, 883, 1035] it has been demonstrated both experimentally and clinically that in acute malaria infections anoxia results from parasitic destruction of the red cells and from an acidosis which further decreases their oxygen-carrying capacity. Monkeys infected with *P. knowlesi*, at different stages of the infection were treated with oxygen, with immediate and spectacular improvement in their general condition. This improvement lasted while the animals were in the oxygen chamber, in spite of the steadily increasing parasitaemia; on withdrawal from the oxygen chamber the monkeys rapidly collapsed. In other cases, entry of the animals into a chamber containing approximately a 40 per cent. concentration of oxygen, together with quinine treatment, was found beneficial; the oxygen served as a supportive measure until the quinine destroyed the parasites. Yet again, combined quinine treatment, transfusions of human blood, and entry into an oxygen chamber, greatly prolonged the lives of monkeys moribund from *P. knowlesi* infections.

The blood transfusion and oxygen treatment of malaria is based on sound physiological principles. Capillary occlusion with petechial haemorrhages is found in various organs in *P. falciparum* infections; this is due to a stagnant anoxia with increased permeability of the capillaries, which leak their fluid

content into the surrounding tissues, so producing haemo-concentration. Why these lesions should occur in one case in the brain and in another in the lungs or the heart is not known. Nicotinic acid causes dilatation of the cerebral capillaries, and "aids in restoration of respiratory systems"; it has been used both alone and in conjunction with oxygen in the treatment of *P. falciparum* infections in man, with rapid relief of symptoms [this *Bulletin*, 1944, v. 41, 536; 1947, v. 44, 495.] Transfusions, oxygen, and nicotinic acid are only adjuvants to the specific drug treatment of malaria, but they may support the patient until this has time to act. *A. R. D. Adams*

VINCKE, I. H. & LIPS, M. Un nouveau plasmodium d'un rongeur sauvage du Congo, *Plasmodium berghei* n. sp. [*Plasmodium berghei*, **a New** *Plasmodium* **of a Wild Rodent in the Belgian Congo.**] *Ann. Soc. Belge de Méd. Trop.* 1948, Mar. 31, v. 28, No. 1, 97–104, 14 coloured figs. on 1 pl.

A new *Plasmodium* (*P. berghei*) from Congo tree rats is described. The rats belonged to at least 5 species, including *Thamnomys surdaster*: 14 out of 93 rats showed parasites in the blood. The infection can be transferred with ease to white mice and to rats (*R. r. frugivorus* and *alexandrinus*), in which animals it causes a heavy parasitaemia followed by death between the 11th and 15th days. In inoculated wild rats, the infection as a rule is less severe. There is enormous enlargement of the spleen and liver, which are heavily pigmented.

The blood of infected animals shows ring forms usually with one chromatin dot, followed by schizogonic forms. When mature, these divide into 6 to 20 merozoites surrounding a central mass of black pigment. Macro- and microgametocytes are produced; these have fine black pigment and measure 7 to 8μ in diameter. The most characteristic features of the parasites are two—the frequency with which multiple infections of the erythrocyte occur and the gross enlargement of this cell. Sometimes six rings are found in a single cell and the cytoplasmic masses are apparently continuous. The absence of pigment is about the only feature which enables such forms to be distinguished from schizonts. The diameter of the rat's corpuscles is normally between 5 and 6·5μ; infected corpuscles enlarge to 10·6μ. Stippling does not occur.

The insect vector of *P. berghei* is most probably *Anopheles dureni*; common anophelines (*e.g.*, *A. gambiae*) of the region failed to transmit it. Before the discovery of this parasite, *A. dureni* had often been found infected with sporozoites in the salivary glands (7 per cent. rates). It had been found in large numbers gorged with blood, in the tree canopy of the forest near Elisabethville. The blood was mammalian but rarely or never human, dog, cat or antelope. The authors therefore looked for an animal host prevalent in the forest canopy and they incriminated the tree rats, a successful climax to a very intelligent piece of field work. During the 1947–1948 season, *A. dureni* failed to show infections in the glands (out of 1,203 examined) and so far sporozoite transmission from this mosquito to the rat has not been made. Parasites resembling *P. berghei* have, however, been found in the gut of wild-caught *A. dureni*, and in one case the contents of the gut, when inoculated into a white mouse, gave rise to a fatal infection due to a parasite apparently identical with *P. berghei*. *P. C. C. Garnham*

RIGDON, R. H. & ROSTORFER, H. H. **Observations on the Anemia in Ducks infected with** *P. lophurae*. *Blood*. 1947, May, v. 2, No. 3, 244–55, 5 figs. [15 refs.]

This paper is written in a confused and, it must be confessed, somewhat confusing manner. Thus, at the beginning of the section "Experimental",

reference is made to figure 1 as demonstrating the parasitaemia and anaemia in a "typical malarial infection in a fatal case." The height of parasitaemia is shown in the figure as occurring on the 7th day, yet, a few lines below the words quoted above comes the statement, "In these ducks the peak of the parasitaemia is reached on the fifth day."

The authors' conclusions would appear to be that the anaemia caused by *P. lophurae* in ducks is due to destruction of mature erythrocytes and the replacement of the latter by erythroblasts which are poor carriers of oxygen. The rapid diminution in the number of parasitized cells after the peak of the infection is considered to be due to the fact that the erythroblasts are relatively unsuitable to the needs of the parasite and do not become parasitized.

H. E. Shortt

GINGRICH, W. D. **Duration of Immunity to Malaria** (*Plasmodium cathemerium*) **in the Canary.** *J. National Malaria Soc.* 1948, June, v. 7, No. 2, 109–17, 6 figs.

This account of the duration of immunity to *Plasmodium cathemerium* in the canary is based on the reactions of canaries, cured of blood-induced infections by anti-malarial drugs, to inoculations of the homologous strain of the parasite.

These inoculations were made at monthly intervals in two series, in one of which each bird received 500,000 and in the other 10,000,000 parasites. Controls consisted of (*a*) birds with latent infections, and (*b*) normal birds.

The conclusions drawn by the author from the experiments were based on three criteria: (*a*) increasing or decreasing parasitaemia after the test inoculation; (*b*) the degree of parasitaemia produced; and (*c*) the duration of the patent parasitaemia.

These conclusions may be summarized by stating that the birds showed a progressive decline in their acquired immunity from the first month after cure until the sixth month, with a total extinction of immunity after eight months.

H. E. Shortt

See also p. 985, SMITH, STEELE, EAKIN & COWIE. **The Tissue Distribution of Radioantimony inhaled as Stibine.**

BLACKWATER FEVER

TISSEUIL, J. La bilieuse hémoglobinurique en 1942 dans les troupes stationnées au Soudan, en Guinée et Côte d'Ivoire. [**Blackwater Fever in 1942 in Troops stationed in French Sudan, Guinea and Ivory Coast.**] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 3/4, 173–6.

In 1942 there were 98 cases of blackwater fever in a population of about 4,000 Europeans in Central French West Africa; there were no cases among an indigenous population in the same region, which numbered about 20,000. Most cases occurred in the second half of the year, which was the epidemic season of malaria, and most of those affected were in some form of active employment. Blackwater fever was common among those who were in the habit of treating themselves with quinine during an attack of malaria. In 1942, quinine was used as a suppressive during the first half of the year and prémaline during the second half; quinine was used throughout the year in small isolated posts. Neither drug was, however, apparently taken regularly. In two districts, the maximum incidence of blackwater fever occurred during the first half of the year when quinine was being taken. In the second half

of the year when prémaline was distributed the number of cases was reduced, especially where the drug was correctly taken. Thus, in Camayenne near Goléah and Konakry, malaria was as severe as in neighbouring areas, but in 70 Europeans there was not one case of blackwater fever. In this district prémaline was taken correctly, while in Goléah, where quinine was being administered, two Europeans out of five developed blackwater fever.

Blackwater fever during 1942 was very severe. Out of a total of 37 deaths among Europeans, 28 were due to it. Classical treatment was not very effective, the death rate ranging from 15 to 35 per cent. Attempts to prevent the development of blackwater fever included monthly systematic splenic examinations of all Europeans. All those with palpable spleens were given the following treatment :—quinine 1 gm. daily for 2 days ; quinacrine 300 mgm. daily for 5 days. The taking of suppressive drugs daily was insisted upon and maintenance of drug suppression was ordered for 15 days to three months after the subject left the endemic area. *B. G. Maegraith*

LEFROU, G. Considérations sur l'étiologie de la fièvre bilieuse hémoglobinurique à propos de 123 cas observées au Soudan. [**Observations on the Aetiology of Blackwater Fever, arising out of 123 Cases in French Sudan.** *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 3/4, 176–87.

This is an account of the results of an enquiry which originated as a result of the unusually high incidence of blackwater fever in French Sudan during 1942 and 1943. Most of the cases referred to were treated in hospital at Bamako and this study, together with previous records, covers 82 patients from 1943 to 1946, including 72 males, 10 females ; 6 were children from 2 to 10 years of age. The incidence of blackwater fever was seasonal, the maximum number of cases occurring during the warm rainy period, particularly in September when *P. falciparum* malaria was most prevalent. Cases were very rare during the hot dry season. Of 100 cases investigated, 20 had lived in the district for one year, 39 for two, 22 for three and 19 for four or more years. The author concludes that there is no obvious relation between the length of stay and the onset of blackwater fever. There were 8 subjects who developed blackwater fever within the first six months of their tour, all of whom had lived previously in Africa. Three cases occurred among new arrivals in Africa within the first year. The severity of the attack increased with the length of stay, the mortality after three or four years being considerably higher than that after one or two years. Over the period discussed there were only six recorded cases of blackwater fever in Africans.

Since the introduction of controlled suppressive antimalarial drug treatment, blackwater fever has become rare in French Sudan. The abrupt rise in incidence in 1942 was probably related to irregular quininization, resulting from difficulty in obtaining supplies in that year. The author emphasizes the danger of prescribing or taking quinine indiscriminately and irregularly. Blackwater fever developed in some cases during the administration of quinine either orally or parenterally for the treatment of a current attack of subtertian malaria. It was never observed in those taking regular quinine prophylaxis. Haemoglobinuria sometimes appeared in persons suffering from malaria who have never taken quinine, *e.g.* in members of the indigenous population.

The author includes chilling, and emotional disturbances among possible predisposing factors. *B. G. Maegraith*

MAEGRAITH, B. G. **The Syndrome of Renal Anoxia in Malaria and Blackwater Fever.** *An. Inst. Med. Trop.* Lisbon. 1947, Dec., v. 4, 427–45, 4 figs. [33 refs.]

A lecture given at the Institute of Tropical Medicine, Lisbon.

TRYPANOSOMIASIS

EAST AFRICA HIGH COMMISSION. **Fauna of British Eastern and Central Africa. Proceedings of a Conference held in Nairobi on 8th and 9th May, 1947.** Paper No. 1. 74 pp., 1 folding map. 1948. Nairobi: Govt. Printer. [Sh. 2/50.]

The conference appears to have limited its discussion almost entirely to the large mammalia often described as "game"; the case for conservation and measures for increasing and maintaining a stock, and also the medico-veterinary objections to game animals as spreaders of infections were fully considered. It is clear that the members of the conference were able to take broad and well-informed views on a very complex matter. The members of the conference, which was called by the East African Governors' Conference, represented British Commonwealth territories from South Africa to the Sudan.

The proceedings give an impression that a serious attempt has been made to collect facts and to consider them. But as each Government submitted a statement beforehand, and also publishes its comments on the resolution passed at the Conference, it is not easy to obtain a consecutive picture of any topic: the same subject recurs at intervals.

Turning to matters of direct interest to readers of this *Bulletin*, we should quote two of the resolutions which were adopted.

"*3-Fauna, Tsetse Fly and Trypanosomiasis*:

"The Conference recognized that under conditions which prevail in Southern Rhodesia the eradication of fauna is a proved method for getting rid of *G. morsitans*, but not of other species of tsetse fly which in many cases are of equal or greater importance. This method of fauna destruction should, therefore, be tested under more varied conditions, at least until other methods of getting rid of *G. morsitans* are available. Experiments now in progress or planned, such as discriminative clearing of bush, controlled burning of bush, and large scale application of insecticides, may provide alternative and better methods.

"The Conference emphasized (*a*) that since the clearing of fly is of little value unless full use is made of the land cleared, plans for efficient land use should be worked out before measures for the eradication of fauna and fly are undertaken, (*b*) that uncontrolled and unsupervised slaughter of fauna is of little use because the animals are reduced thereby to an insufficient degree. Consequently the destruction of game must be undertaken by experts under proper control, that is, under the aegis of game departments.

"*4-Fauna and Animal Disease* (*other than Trypanosomiasis*):

"In view of the part played by wild animals in the spread of diseases of domestic species (rinderpest, foot and mouth disease, east coast fever, anthrax, African swine fever, mange and rabies, etc.), provision should be made for veterinary control of game areas, either by very close co-operation between Game and Veterinary departments or by posting veterinarians to game departments or the staff of national parks.

"In order to limit the spread of disease by wild animals, game reserves, national parks and other game areas should be isolated wherever feasible, so that movement of the larger species, especially ruminants, from one game area to another could be prevented."

In the Appendices, E. B. WORTHINGTON (Scientific Secretary to the East African Governors' Conference) discusses what should be the policy with regard to wild animals in view of the increasing human population, and urges that game departments should be staffed so as to be able to make a zoological study of the animals. P. A. BUXTON gives a general summary of the "Relation of

Tsetse Flies to Game." H. FAIRBAIRN emphasizes the view that game is a reservoir for *Trypanosoma rhodesiense*, and again sets out the evidence. Sir Guy MARSHALL states the contrary view.

A map, extending from the Sudan to Southern Rhodesia shows National Parks (existing or proposed), Game Reserves and controlled areas. The area at present reserved is just over one million square miles, 6·9 per cent. of the total area of the British territories. *P. A. Buxton*.

BRITISH MED. J. 1948, June 26, 1249. **Tsetse Fly Problem in Africa. Stephen Paget Memorial Lecture** [Buxton, P. A.].

In this lecture, Buxton sums up on broad lines the knowledge that has been gained on tsetse flies and means of controlling them. For control of water-side tsetse hand-catching and clearings of various kinds are important, the successful experiment at Anchau (Nigeria) is a pointer to probable future effort. For the game flies clearance of vegetation, destruction of game, and human settlement in cleared areas have their place. Insecticides might be effective in small areas, but could hardly be applied over large tracts of land.

The lecture is a conspectus and an opinion; Buxton has returned from several journeys through Africa feeling reasonably optimistic about the tsetse situation. *Charles Wilcocks*

NASH, T. A. M. **Tsetse for Tyros.** 18 pp., 2 pls. Medical Department, Nigeria. 1948. Lagos: Govt. Printer.

Dr. Nash has written this little booklet in very simple English. He hopes it will be understood by Africans with educational qualifications as low as Middle II. Some parts are useful to doctors, veterinary officers and others interested in tsetse flies. He describes first how flies of the genus *Glossina* may be distinguished from other flies, and then gives the characters for the recognition of the different species found in Northern and Southern Nigeria. The life history of the tsetse is described and clear instructions are given for collecing adults and pupae. There is also a brief account of different types of vegetation and methods of control, and some hints on how to avoid being bitten. The two plates illustrate the fly, its antennae, the pupa and the abdomens and hindlegs of *Glossina palpalis*, *G. tachinoides*, *G. morsitans* and *G. fusca*.

H. S. Leeson

RAMOS, A. S. & ASSOREIRA, M. Aracnoidite opto-quiasmática tripanosómica e tratamento cirúrgico. Contribuição para o estudo da cegueira da doença do sono. [**Optic Chiasma Arachnoiditis in Trypanosomiasis and its Surgical Treatment. A Study of Blindness in Sleeping Sickness.**] *An. Inst. Med. Trop.* Lisbon. 1947, Dec., v. 4, 33–47, 2 figs. on pls. [11 refs.] English summary.

WEURMAN, C. **Investigations concerning the Symbiosis of Bacteria in** *Triatoma infestans* **(Klug).** Reprinted from *Antonie van Leeuwenhoek*. 1946, v. 11, 129–38, 1 fig. [10 refs.]

MEYER, H. & XAVIER DE OLIVEIRA, M. **Cultivation of** *Trypanosoma cruzi* **in Tissue Cultures: a Four-Year Study.** *Parasitology*. 1948, July, v. 39, Nos. 1/2, 91–4, 17 figs. on 2 pls.

Trypanosoma cruzi has been cultivated by the tissue culture technique by various workers, but the present account describes what is probably the most comprehensive study of *T. cruzi* on these lines. The method employed was Carrel's hanging drop technique.

Several interesting observations are made, among them the curious fact that although the organism was easily maintained in tissue culture in chick embryo material over a period of more than two years, yet living chicks could not be infected with the cultures. Other observations were that the entire cycle—trypanosome, leishmania form, crithidia and back to trypanosome—took place in one cell and the number of trypanosomes produced was proportional to the size of the host cell. No division of adult trypanosomes was observed nor any indication of sexually differentiated forms. [The paper is evidently a condensation of a great deal of original observation which would repay fuller description.] *H. E. Shortt*

LEISHMANIASIS

GIRAUD, P., BERNARD, R. & BERGIER, P. Chronique du kala-azar à Marseille. [**A Review of Kala Azar in Marseilles.**] *Bull. et Mém. Soc. Méd. Hôpit de Paris.* 1947, Nos. 3/4, 61–2.

In 16 years up to 1939, the authors recorded 165 cases of leishmaniasis in the Marseilles area. In the 8 years 1939–1946 they have found 73 more, giving a total of 238. The average number of cases annually for the two periods was thus about the same.

The yearly incidence for the years 1939–1946 is given in a table and shows a sharp drop in 1942–1944, which years only averaged 3 cases. This was followed by a brisk rise in 1945–1946. The authors have not entirely satisfied themselves as to the exact cause of this change. No doubt the dry years 1943 and 1944 were unfavourable to the breeding of the insect vectors and the rainy years 1945 and 1946 (when there were 12 and 17 cases) were favourable to such breeding. The disappearance of many dogs during the wartime period of food shortage would not be sufficient to explain the change in incidence. The authors, however, noted a comparable situation in the endemic rate observed between 1930 and 1935, when there was a similar variation with a maximum of 24 cases in 1932.

Over half the patients were under 3 years of age, and the incidence fell rapidly after 4 years. Three cases were in infants under 10 months, and only one in an adolescent and two in adults. Infection occurred regularly in the suburbs and country districts ; two cases originated in Corsica.

The topographical distribution and incidence in dogs corresponded closely with that in man over the same period. Gland puncture (shoulder) was simple and reliable in dogs [see also this *Bulletin*, 1948, v. 45, 883].

The authors believe on epidemiological grounds that the local endemic is essentially a disease of dogs accidentally transmitted to man by ticks rather than by *Phlebotomus*, and that in general its existence in the French Mediterranean area is constant and stable. It is added that two children with kala azar also had a history of *fièvre boutonneuse*. *H. J. O'D. Burke-Gaffney*

RACHMILEWITZ, M., BRAUN, K. & DE VRIES, A. **Hematologic Observations in a Case of Kala-Azar.** *Blood.* 1947, July, v. 2, No. 4, 381–5, 1 fig. [12 refs.]

"The hematologic findings in a case of kala-azar under the influence of specific treatment are described. The type of the anemia, the hyperplastic bone marrow, the increased urobilinogen output before treatment, and the subsequent changes following treatment strongly suggest increased red cell destruction (most probably by phagocytosis) as the cause of the anemia."

DE AZEVEDO, J. F., TEIXEIRA, A. W. G. & COITO, A. de M. F. Sobre a infestação por leishmanias nos cães de Lisboa. [**Leishmania Infection in Stray Dogs in Lisbon.**] *An. Inst. Med. Trop.* Lisbon. 1947, Dec., v. 4, 99–106.

The English summary appended to the paper is as follows :—

"As a complement to the studies carried out in the Institute of Tropical Medicine on the epidemiology of the kala-azar, the authors have determined the rate of infestation by leishmaniae in vagrant dogs of Lisbon.

"For this purpose, from 1945 to 1947, they searched for leishmaniae directly in spleen, as well as in liver smears of those animals, by culture of these organs (medium NNN) and in bone marrow and nasal mucus smears.

"Out of 137 dogs examined, 9 have been found infected, which gives an infection rate of 6·5 per cent., a percentage considerably higher as compared with those of 3·6 and 2·08 per cent. found by other investigators also in dogs of Lisbon in the periods of 1910–1912 and 1936–1938 respectively. In one of the dogs leishmaniae have been found in the nasal mucus.

"They also observed that the largest proportion of infected animals was found among the oldest dogs and that the infection rate in the females was larger than that of the males."

SMITH, R. E., STEELE, J. M., EAKIN, R. E. & COWIE, D. B. **The Tissue Distribution of Radioantimony inhaled as Stibine.** *J. Lab. & Clin. Med.* 1948, May, v. 33, No. 5, 635–43, 7 figs.

BRADY *et al.* [this *Bulletin*, 1945, v. 42, 747] studied the fate of radioactive trivalent antimony in dogs after intravenous injection. The inhalation of stibine (SbH_3), a gaseous trivalent compound of antimony, was shown by the present authors to cause reduction in the level of parasitaemia of chickens infected with *P. gallinaceum*. This substance containing the metal in radioactive form has now been used to determine the concentration of Sb in the blood and tissues of normal and infected chickens as well as in guineapigs at various time intervals after administration.

The antimony isotopes were prepared by bombardment in the cyclotron and the two forms produced with a half life period of 2·8 and 60 days respectively were used as a mixture for the production of stibine by the action of HCl on the fusion product with magnesium. The animals were exposed to various concentrations in a special chamber for different periods and on removal were bled prior to removal of tissues for estimation of antimony. The radioactivity of samples was measured by means of a *beta* ray counter under standard conditions and the amount of Sb determined with reference to standards. The concentration of stibine in the chamber was approximately 25 parts per million and the time of exposure about 50 minutes.

Haemolysis of red blood cells occurred in some cases. The results obtained with chickens heavily infected with *P. gallinaceum* were not significantly different from those with controls. The concentration of Sb in the blood stream fell off gradually but more rapidly in guineapigs than in chickens. At first there was some localization in red cells but the excess of metal over that in plasma was reduced with time. The concentration in most tissues approximated to those in blood, but in liver and spleen there was a maximum level about 1 hour after treatment, and after four hours the level was higher in liver, spleen and kidney than in whole blood. Antimony appeared to be eliminated at a greater rate by the guineapig than by the chicken. *J. D. Fulton*

FEVERS OF THE TYPHUS GROUP

RABINOWITZ, Esther, ASCHNER, M. & GROSSOWICZ, N. **Cultivation of *Rickettsia prowazeki* in Dead Chick Embryos.** *Proc. Soc. Exper. Biol. & Med.* 1948, Apr., v. 67, No. 4, 469–70.

Living cells were still present in chick embryos 16 days after the latter had been killed, on the third day of development, by chilling at 4°C. for 24 hours and then kept even at a temperature of 37°C.

Rich cultures of rickettsiae were found after 14 days of cultivation in embryonated eggs killed by chilling and inoculated within about seven days. Storage was at room temperature.

Successful cultivation was obtained with rickettsial suspensions containing too few organisms to yield cultures when the usual technique was adopted The special advantage of the method is that the killed embryos can be stored "for some time" and then used like ordinary culture media. The eggs can be inoculated in the field and transported to the laboratory without the special precautions that are needed when living embryos are employed.

John W. D. Megaw

CLARKE, Delphine H. & FOX, J. P. **The Phenomenon of *in vitro* Hemolysis produced by the Rickettsiae of Typhus Fever, with a Note on the Mechanism of Rickettsial Toxicity in Mice.** *J. Exper. Med.* 1948, July 1, v. 88, No. 1, 25–41. [12 refs.]

Suspensions containing sufficient numbers of *Rickettsia mooseri* or *R. prowazeki*, especially when prepared from yolk-sac cultures, were found to cause haemolysis *in vitro* of red blood cells of rabbits and sheep, but not of mice, cotton rats and guineapigs. Suspensions of *R. orientalis* did not haemolyse rabbit cells.

The haemolysin was closely associated with the bodies of living rickettsiae, being present in the sediment obtained by high-speed centrifugation, but not in the supernatant fluid: it was destroyed by formol (0·5 per cent.) and by heating to 56°C. for one hour; its activity in suspensions was parallel with the toxicity for mice, and the infectivity for cotton rats, of the suspensions.

It is thought likely that the degree of haemolytic activity may turn out to be a rapidly observable, though only roughly quantitative, index of the infectivity of suspensions. Homologous antisera inhibit the haemolytic action, which therefore may form the basis of a useful serological test having the special feature of depending on a property of living rickettsiae. The haemolytic factor may possibly be identical with the rickettsial toxin which is known to cause early death in experimental mice.

John W. D. Megaw

SANDOR, G., GIROUD, P. & SKROBISZ, C. Mlle. Etudes des anticorps anti-rickettsiae du sérum de lapin. [**Study of Rickettsial Antibodies in Rabbit Serum.**] *Ann. Inst. Pasteur.* 1948, June, v. 74, No. 6, 518.

In a previous note [this *Bulletin*, 1948, v. 45, 166] the authors discussed the identity of the antibodies produced in rickettsial antiserum and they now present the first results of the application of their technique in distinguishing the antibodies in rabbit serum.

As in the case of normal rabbit serum, sufficient precipitate cannot be extracted by simple dialysis where distilled water is used, at any rate if dialysis is prolonged for only 2 or 3 days. Acidification (optimum about *p*H 5·5), on the other hand, makes it possible to obtain abundant precipitate from dialysed serum diluted one in four. This precipitate accounts for an average of 0·8

per cent. of the serum proteins and can be separated into an insoluble and a soluble protein fraction in about equal parts, in the presence of a dilute phosphate buffer (N/100) at about *p*H 6 : these are euglobulin II B and II A.

The insoluble fraction disperses with difficulty and only in weakly alkaline medium, producing a markedly opalescent suspension. It represents a lipoprotein complex containing about 40 per cent. of lipids consisting entirely of neutral fats. This fraction is devoid of any agglutinating power against rickettsiae.

The soluble protein fraction contains only a small percentage of lipids and gives a completely clear solution. It often accounts for all the agglutinating activity, but a small but variable proportion of this is also present sometimes in the pseudoglobulins.

In rabbit anti-ovalbumin serum or horse antiglobulin serum there is a euglobulin I which contains a small amount of the specific flocculant factor ; but the greater part is to be found in the pseudoglobulins. Common proteins are close to exotoxins antigenically, but viruses differ in this respect. Rickettsiae may be regarded as being comparable with endotoxins or bacterial antigens. Similar results were obtained with STEFANOPOULO in the case of yellow fever antiserum in the horse. *H. J. O'D. Burke-Gaffney*

GAASE, A. Die Thermostabilität der Agglutinine in der Differentialdiagnose von Fleckfieber und Proteusinfektion. [**The Thermostability of Agglutinins in the Differential Diagnosis between Typhus Fever and** *Proteus* **Infections.**] *Ztschr. f. Hyg. u. Infektionskr.* 1948, Apr. 1, v. 127, Nos. 6/8, 730–41, 10 figs. [21 refs.]

Contrary to the findings of some previous workers, the author has found that the agglutinins against *Proteus OX19* are very variable in their resistance against heating. He tested the sera of 220 typhus patients before and after heating to 56°C. for one hour, and found that although heating caused a fall in the Weil-Felix titre in 79·5 per cent. there was no change in 13·2 per cent. and there was actually a rise in 7·2 per cent. In 68·6 per cent. of the cases, the titre after heating remained at a height of 1–400 or over.

In a case of furunculosis due to *Proteus vulgaris*, the patient's serum did not react to *Pr. OX19* ; neither did the serum of any of 10 guineapigs which had been immunized against 10 different strains of *Pr. vulgaris*, although several of these strains were agglutinated by the sera of typhus patients. These findings are regarded as additional evidence of the specificity of the Weil-Felix test for typhus fever.

The agglutinins of the above guineapigs against homologous strains of *Proteus* organisms showed a higher average degree of thermostability than was shown by the agglutinins of typhus patients against *Pr. OX19*, yet there was a fall in the titre in 43·9 per cent. of the cases after heating, so that the thermostability of the agglutinins in the Weil-Felix reaction cannot be regarded as supporting the diagnosis of *Proteus* infection as opposed to that of typhus fever. *John W. D. Megaw*

BRISOU, J. & AUTHEMAN, R. Diagnostic du typhus par réaction de fixation du complément. Etude de divers antigènes. [**The Diagnosis of Typhus Fever by the Complement-Fixation Reaction. A Study of Various Antigens.**] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 3/4, 112–14.

In a trial of various antigens prepared from typhus vaccines the best results were obtained with a formolized vaccine of the Durand-Giroud type, preferably less than one year old.

The vaccine was centrifuged at 4,000 revolutions for half an hour and the sediment was resuspended in normal saline solution. *John W. D. Megaw*

LÜBKE, A. Perakutes Fleckfieber nach Milzentfernung. [**Fulminating Typhus Fever after Splenectomy.**] *Med. Klin.* 1947, June, v. 42, No. 11, 459–61.

A description is given of a fulminating attack of typhus fever which occurred in a young man whose spleen had been removed three years previously because of disorganization by a shell splinter. The patient had been perfectly healthy except for a slight feeling of lassitude for a few days before the onset, which was very sudden and was followed by death within 18 hours. The rash appeared two hours before death; it rapidly became haemorrhagic. The fulminating nature of the illness was attributed to the loss of the protective influence of the spleen. *John W. D. Megaw*

FRANK, H. R. & MAY, K. H. Zur Wirkung menschlicher Rekonvaleszentenseren auf murines und klassisches Fleckfiebervirus. [**The Action of Human Convalescent Serum on Murine and Classical Typhus Infection.**] *Ztschr. f. Hyg. u. Infektionskr.* 1948, Apr. 1, v. 127, Nos. 6/8, 489–95, 2 figs. [16 refs.]

The potency of samples of serum taken from typhus convalescents was tested by mixing 0·5 cc. with 10,000 minimal infective doses of brain substance of mice infected with murine typhus, and injecting the mixture intraperitoneally into mice. Only three mice were used in testing each sample, and the results obtained were exceedingly varied. A mixture of the serum of two convalescents was tested on the 8th, 16th and 32nd days after defervescence: the first sample gave complete protection to all the mice; the second was completely useless, two of the mice died within 48 hours and the third on the 9th day; the third sample gave complete protection to one mouse and partial protection to the only other one used in this test.

Of the 17 mice employed in testing six samples of serum taken between the 8th and 41st days, six remained healthy, two had abortive attacks, one recovered after a severe attack, and eight died.

Each of the six samples of serum was tested by inoculating a guineapig with a mixture of the serum and a suspension of the brain of a guineapig infected with classical typhus; all the guineapigs developed febrile reactions which were somewhat less severe than that of a control animal, and the degree of protection observed is stated to have corresponded with the results of the previous test.

The authors state that a potent serum remains fully effective after storage for two months, and, when carbolized after storage for three months.

The above method of testing is regarded as the best available for estimating the value of convalescent serum. *John W. D. Megaw*

SIEGERT, R. Fleckfieberimmunität und Schutzimpfung. [**Typhus-Fever Immunity, and Protective Inoculation.**] *Ztschr. f. Hyg. u. Infektionskr.* 1948, Apr. 1, v. 127, Nos. 6/8, 512–20, 2 figs. [14 refs.]

The "Henderson test" [see this *Bulletin*, 1946, v. 43, 20] is regarded by the author as a valuable means of estimating the degree of antitoxic immunity possessed by the sera of persons who have recovered from attacks of typhus fever or who have been inoculated against the disease. The test is based on the amount of serum needed to protect mice against early death after injections of rickettsial toxins.

The author found that the antitoxic titre of persons recovered from attacks of typhus fever was at least eight times higher than that of inoculated persons. He also found that the antitoxic titre varied from less than 1–2 to 1–32 among four guineapigs fully protected against infection by the same doses of vaccine. He regards the antitoxic factor as being of great importance in the production of immunity in inoculated persons and recommends that tests for this factor as well as for the anti-infective factor should be carried out at intervals on persons exposed to risk of laboratory infection. *John W. D. Megaw*

MacCarthy, Ethna. **Public Health Problems created by Louse Infestation.** *Irish J. Med. Sci.* 1948, Feb., 6th Ser., No. 266, 65–78, 2 figs. & 4 maps. [14 refs.]

See *Bulletin of Hygiene*, 1948, v. 23, 798.

Montoya, J. A. & Osejo, P. P. **Studies on the Use of DDT and Phenyl Cellosolve for Control of Pediculosis in Villages in Colombia.** *Amer. J. Hyg.* 1948, May, v. 47, No. 3, 247–58, 2 figs. [13 refs.]

In two primitive highland villages in Colombia experiments were made to determine, first the minimum frequency of application of DDT (against body lice) and phenyl cellosolve (against head lice) to maintain the louse infestation index at a sufficiently low level to render unlikely the transmission of typhus; secondly, to determine the interval required after one application for the infestation to reach its original level.

A complete census of the villages was made before the experiments started and showed that one had a population of 586 and the other 1,261. The people were also prepared for the investigation by an educational campaign. Against body lice, all persons were dusted with 10 per cent. DDT in pyrophyllite or talc applied by hand dusters, while powder sifters were used for bedding, etc. Against head lice, the phenyl cellosolve was applied in the form of a scented shampoo consisting of phenyl cellosolve 5 parts, ethanol 47·5 parts and distilled water 47·5 parts. Between January, 1946, and January, 1947, ten surveys were made in the first village and on five of these occasions treatment was given. Nearly 100 per cent. of the population received four treatments and 66 per cent. received all five treatments. After the two initial applications, one week apart, the body louse infestation rate fell from 58·9 per cent. to less than 5 per cent. and remained so for four months. The head louse rate followed a similar course.

In the other village, there were seven surveys but only one treatment, which 98·2 per cent. of the population received. The body louse infestation rate which started at 76·7 per cent. fell steadily to 1·5 per cent. in May, but after ten months it had risen to 60 per cent. when the experiment was terminated. The head louse infestation rate behaved similarly.

Among 101 treated children in school (37 of whom came from rural areas which had not received treatment) the infestation rate among the urban children closely approximated to that of the general village population, but the rural children became reinfested from their untreated homes and their rates remained high.

Although it is unknown at what level of louse infestation the danger of typhus becomes negligible in primitive communities, it is considered, on the basis of these experiments, that 5 per cent. represents a reasonable upper limit to set for such communities in Latin America. To maintain the rate at or below this level will necessitate treatment of at least 98 per cent. of the population every four months.

One team, consisting of a sanitary inspector and a nurse, working 8 to 10 hours a day, can do an average of 17 residences, giving 102 treatments and examinations ; without examination, the team can do 180 people per day. The treatment costs very little and takes 2·25 ounces of 10 per cent. DDT for one person and his bedding, etc., and one ounce of phenyl cellosolve lotion per woman and 0·5 oz. per man.

No toxic effects were observed among the treated persons or the operators.

H. S. Leeson

ESKEY, C. R. & HEMPHILL, F. M. **Relation of Reported Cases of Typhus Fever to Location, Temperature, and Precipitation.** *Pub. Health Rep.* Wash. 1948, July 16, v. 63, No. 29, 941–8, 4 figs.

Most of the information contained in this survey of the incidence of murine typhus fever in the U.S.A. is presented in the form of graphs and a map. The total number of cases reported during the period 1913–1944 was nearly 36,000, of which almost 95 per cent. occurred in eight southern States.

Owing chiefly to the increasing recognition of the disease, 60 per cent. of the cases were reported in the last six years of the above period. [The statement in the body of the paper that 60 per cent. of all the cases occurred during the 31-year period is obviously due to a typographical error.]

The disease is concentrated in the zone between 31° and 33° north latitude, especially towards the south of the zone. Fewest cases occurred during the winter and spring months ; August, July and September were the months of highest prevalence. The number of cases reported annually increased every year except in 1940 when the number was smaller than in 1939. This departure from the trend is regarded as being due to the exceptionally cold weather experienced in January, 1940. There was no significant degree of association between rainfall and rate of incidence. *John W. D. Megaw*

CALLOT, J. & VENDRELY, R. Essais d'action enzymatique sur des micro-organismes du groupe des *Rickettsia.* [**Studies on the Action of Enzymes on Rickettsiae.**] *C.R. Soc. Biol.* 1948, Mar., v. 142, Nos. 5/6, 396–7.

The authors have applied a method called enzymatic analysis to the study of the cytological structure of rickettsiae. The method has already been employed in the investigation of bacterial cells by BOIVIN whose paper on the subject was still in the press at the time of writing.

Rickettsial smears were fixed in absolute alcohol, then treated for varying periods up to two and a half hours by solutions of one of the two enzymes, ribonuclease and desoxyribonuclease. The smears were washed and stained by Giemsa's stain.

Striking results were obtained by treating the smears with the latter enzyme, especially in the case of *Rickettsia pipientis* obtained from the ovaries of infected *Culex pipiens.* After prolonged applications the rickettsiae ceased to take on the stain.

Smears of *R. mooseri* from infected guineapigs were also affected, though to a lesser degree, but they had not been freshly prepared.

The findings were regarded as supporting the view that rickettsiae are intermediate in structure between bacteria and filterable viruses.

Reference is made to the work of TOVARNICKIJ *et al.* [*Nature*, 1946, Dec. 21, 912] who have found that the chemical composition of *R. prowazeki* is intermediate between that of bacteria and viruses. *John W. D. Megaw*

PHILIP, C. B. **Tsutsugamushi Disease (Scrub Typhus) in World War II.** *J. Parasitology.* 1948, June, v. 34, No. 3, 169–91, 1 map. [30 refs.]

This paper consists chiefly of a critical review of the new knowledge of tsutsugamushi disease gained in the course of the Asiatic-Pacific campaign of 1941–1945. Most of the papers referred to by the author have been dealt with in this *Bulletin* and as the article is a summary it does not lend itself to the preparation of an abstract.

A few points of special interest are as follows :—The allied forces escaped several major disasters solely because there did not happen to be any action by the enemy at the times and places of occurrence of large outbreaks of the disease, and it was only because of the prompt and energetic action taken by the allied experts to discover and apply effective measures of control that serious interference with the campaign was avoided.

Although the closely related *Trombicula akamushi* and *T. deliensis* are the only proved vectors of the disease, about 100 new species of Trombiculidae (" chigger mites ") have been discovered since 1940—mostly in the Eastern Hemisphere. Despite numerous references in the literature to " blood meals " the larval mites do not ingest blood, but only lymph and tissue fluids. The larvae do not remain attached to the animal hosts for more than three or four days, so that they have never been found attached to the subsequent eschars on patients.

The chief reservoirs of infection of the mite-borne, as of the tick-borne, fevers of the typhus group are believed to be the arthropod vectors ; the vertebrate hosts are now regarded as being transitory reservoirs.

The correct nomenclature of the agent is discussed ; the name *Rickettsia orientalis* was first applied in 1930, by Nagayo *et al.* who had also referred seven years earlier to its apparent rickettsial relationship. The author, however, considers that the name *R. tsutsugamushi* " will be most generally adopted ", for the following reasons :—(1) Hayashi, in 1920, described a protozoon, which he called *Theileria tsutsugamushi*, as the cause of the disease ; (2) Various Japanese writers have stated that Hayashi " must have seen rickettsiae in some of his 1920 preparations " so that his specific name by generic transfer deserves acceptance. [Yet the earlier name *Rickettsia nipponica* applied by Sellards is considered inadmissible because its sponsor wrongly reported that he had cultivated the agent.]

The author refers to the pseudo-typhus of Sumatra : like most other workers he has overlooked the fact that the disease referred to should be called pseudo-typhoid when translated into English.

The very puzzling differences in the antigens of various strains of the agent are discussed, and mention is made of a patient whose complement-fixation titre against a New Guinea antigen was 1–512, whereas against a Burmese antigen the reaction was negative.

A useful map, dated 1946, shows the known geographical distribution of mite typhus.

Apart from the influence of combat fatigue and other depressing factors, which caused an increase in the fatality rate, there was evidence of astonishing differences in the virulence of the infection in various localities ; for example among 1,469 cases at Owi Biak the fatality rate was only 0·6 per cent., but in smaller outbreaks in Goodenough Island and Finchhaven the rates were 27·5 and 35·3 respectively, despite hospital care and the absence of adverse conditions.

A bibliography, described as partial, contains 30 references. In this short paper of 23 pages the author has succeeded in presenting a clear description of the special features connected with the epidemiology and control of the disease as observed during the second world war. *John W. D. Megaw*

SHEPARD, C. C. & HUEBNER, R. J. **Q Fever in Los Angeles County. Description of some of its Epidemiological Features.** *Amer. J. Pub. Health.* 1948, June, v. 38, No. 6, 781–8.

By this careful epidemiological study the authors have confirmed and extended the findings of previous workers in the U.S.A., but although the disease in man seems to be definitely associated with contact with cattle, the mode of transmission, especially to the infected cattle, remains a matter for speculation. Proof is still lacking that human infection is acquired from cattle; the authors think it possible that cows and human beings may be infected from a common source.

No evidence of transmission by ticks has been found in any of the American outbreaks.

The authors investigated 17 cases which occurred within 10 to 30 miles of the City of Los Angeles in an area in which there were large numbers of dairies where the cows were kept continuously in pens because of the lack of pasture. Eleven of the cases occurred within a period of seven weeks during April and May, 1947. The usual hospital diagnosis was atypical or virus pneumonia; pneumonitis was detected in all the cases investigated by X-rays. The complement-fixation titre reached a height of 1–64 or over in every case, and *Rickettsia burneti* was isolated from four patients by guineapig inoculation.

All but two of the patients had either visited dairies or had lived near them, though none had been employed in a dairy or had immediate contact with cows.

Sera of 20 dairy workers in the area were tested; ten reacted at titres of 1–4 to 1–32, though none gave a history pointing clearly to the previous occurrence of an attack of Q fever.

Sera of 166 other persons living in the area, but not connected with the dairies, were tested; five reacted at titres of 1–4 to 1–16.

Sera of 96 persons living in the District of Columbia were all negative. Sera of 130 cows from nine dairies in the area were examined; 21 were positive, ten of them at titres of 1–64 or over.

The findings suggest that Q fever, usually in a mild form, frequently occurs among the cattle, dairy workers, and residents near the dairies of the area.

In an Addendum it is stated that since this paper was submitted for publication HUEBNER *et al.* have reported the finding of *R. burneti* in raw milk from four dairies in South California [see this *Bulletin*, 1948, v. 45, 509. The authors of the present paper were also two of the four authors of the above-mentioned report]. *John W. D. Megaw*

YELLOW FEVER

CAUSEY, O. R., LAEMMERT, H. W., Jr. & HAYES, G. S. **The Home Range of Brazilian Cebus Monkeys in a Region of Small Residual Forests.** *Amer. J. Hyg.* 1948, May, v. 47, No. 3, 304–14, 3 figs.

Jungle yellow fever in Brazil appears either in an enzootic form in the tropical rain forests or an epizootic form in sparsely wooded areas of the central and southern regions. Because no evidence had been obtained that either birds or some species of bats are responsible for the spread of the virus over sparsely wooded country during epizootics, the present investigation of the rôle of sylvan primates was undertaken.

The region chosen for study was Passos, Minas Gerais, which lay in the path of the epidemic which, during the periods from 1934–1940, swept south from the Amazon watershed. A similar epidemic appeared in 1944 which began to

retrace the path followed 10 years previously. A field laboratory was, therefore, established in front of the epidemic with the intention of initiating investigations before the virus actually arrived.

The country around Passos is characterized by large open pastures. The forested areas are for the most part limited to the steeper hilltops and deeper ravines, where may be found the remnants of climax and young-type forest. These wooded areas are frequently isolated from one another by one or two kilometres of pasture or they may be connected by marginal growth along streams.

During the study, which lasted 15 months, 1,025 monkeys were captured. 62 per cent. were taken more than once. Only one animal was found more than 1,000 metres from his home forest and less than 3 per cent. of recaptured specimens were known to have travelled distances of 100 to 800 metres across open country.

In a large forest, where there was a number of bands of *Cebus* monkeys, it was rare to find one band wandering into the territory of another.

Thus, the normal movements of *Cebus* monkeys do not appear to explain the rapid and extensive spread of yellow fever through the sparsely wooded areas of central and south Brazil. *F. O. MacCallum*

DENGUE AND ALLIED FEVERS

McCarthy, D. D. & Wilson, D. Bagster. **Dengue in the East African Command. Incidence in relation to *Aëdes* Prevalence and some Clinical Features.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1948, July, v. 42, No. 1, 83–8.

This paper deserves attention because of the emphasis laid by the authors on the extreme variability of the manifestations of dengue, a feature which they rightly regard as being responsible for frequent failures to recognize the disease. Only occasional cases had been previously diagnosed in the civilian hospitals of British East Africa; and in the Command itself the diagnosis was rarely made except when an epidemic occurred.

The disease was specially prevalent in Dire Dawa and Harrar in Ethiopia; Mogadishu in Somalia; Diego Suarez in Madagascar; and Mayotte in the Comoro Islands. Cases also occurred in other places in Somalia, in British Somaliland, at Mombasa, and in Mauritius.

At Diego Suarez, the incidence among European units in 1943 was more than 100 per cent., but the rate for all races was only 12·3 per cent. The difference in incidence is attributed to difficulty in recognizing the rash and other features of the disease among Africans. [No mention is made of the probable influence of immunity resulting from previous attacks.]

At Diego Suarez in 1942 many cases were diagnosed as sandfly fever, although *Phlebotomus* was completely absent from the area: here and at Mogadishu the French and other residents regarded the yearly outbreaks as due to influenza.

Severe pains did not occur. A rash, sometimes lasting only one or two hours, was seen in nearly half of the European patients, but a fully developed rash, rubeoloid or an erythematous background, was seen in only 20 per cent. Dusky redness of the fauces and palate was frequently seen. An alteration of the sense of taste was common, and in some mild cases was the only symptom of which the patients complained.

In 25 per cent. of the cases one lymphatic gland or one group of glands was enlarged; generalized lymphadenitis was never seen. Typical saddle-back

temperature charts formed only 10 per cent. of the total; continued, remittent and intermittent types of fever were equally common; a fall of temperature by crisis was the most constant feature of the illness. The pulse was about 100 per minute at the onset; soon the rate fell to about 70.

Leucopenia was usually pronounced by the 4th day.

The disease is described as being "amazingly variable in its clinical manifestations, with no predominant symptom recurring as characteristic, each symptom taking its turn as the dominant feature."

At Mogadishu, the reduction of the *Aëdes* index from 27 per cent. to 10 per cent. caused almost complete control of the disease: at Diego Suarez, control was not effective till the index fell below 2 per cent.

John W. D. Megaw

PLAGUE

SANDOR, G., GIRARD, G. & SKROBISZ, C., with the collaboration of A. CHEVALLIER. Etude du sérum antipesteux de cheval. [**Study of Plague Antiserum in the Horse.**] *Ann. Inst. Pasteur.* 1948, June, v. 74, No. 6, 516–17.

The authors have previously shown that the plague bacillus does not possess a true exotoxin [this *Bulletin*, 1947, v. 44, 900]. The present note brings the matter farther in discussing a study of the antiserum produced by the injection of plague bacilli or toxoid. While *P. pestis* contains purely protein antigens which are chemically related to exotoxins, it is shown, on immunological grounds from the behaviour of the euglobulin fractions produced, that plague antiserum is of the antibacterial and not of the antitoxic type. As the senior author, and also POPE (*Brit. J. Exper. Path.*, 1938, v. 19, 245) have shown, antitoxins resist proteolysis in a weakly acid medium, followed by selective coagulation. In plague antiserum this resistant fraction is absent. The antigens of *P. pestis* are not exotoxins or true toxins but, simply, "bacterial antigens".

H. J. O'D. Burke-Gaffney

CHABAUD, A. G. Les arthropodes vecteurs de la peste bubonique. [**Arthropod Vectors of Plague.**] *Ann. Parasit. Humaine et Comparée.* 1947, v. 22, Nos. 3/4 & 5/6, 169–200; 357–79. [Numerous refs.]

The Indian Plague Commission of 1907 to 1912 confirmed the findings of the Royal Plague Commission of 1898, previous workers, and subsequent workers: that plague was transmitted to man by fleas of the domestic rat. The problem has widened considerably since these fundamental investigations were carried out and especially with the introduction into it of sylvatic plague and its dangers. The author has compiled a reference work of great utility. He puts forward as a possibility in the epidemiology of plague three distinct cycles: (1) In wild rodents, (2) in domestic rodents, and (3) in man alone.

The first article deals only with wild rodent sylvatic plague. A wealth of information on host species, geographic foci, vector agents, together with reference to authority, is given in a table, listing altogether 111 rodent species. Besides rodents a number of wild animals are attacked by plague; among the primates are *Semnopithecus entellus* and *Macacus radiatus*. The siphonapterous parasites of the rodents are all listed in the table. A considerable text, with details of efficiency of transmission precedes the table and represents much labour.

In the second article dealing with the domestic rodent cycle and the human cycle, the same careful treatment is followed. A second table is given under the heading "spontaneous or experimental infection and experimental transmission of plague by fleas", with columns for species (71), chief host, spontaneous or experimental infection, experimental transmission and authority.

In his summary, the author concludes that "an arthropod can be efficient in the transmission of plague from one Citellus to another but incapable of transmission to an animal of another group". . . . "It is now recognized that all the siphonaptera can become plague infected, but are often described as not pestigerous". In no case, however, has the author found a flea incapable of transmission where the following were fulfilled: (1) a good crop of fleas. (2) The use of the host preferred by the insect. Anatomical considerations may also play a part in transmissibility of plague.

This work is very systematic, and comes from, and with the authority of, Brumpt's Institute in Paris. *W. F. Harvey*

TOUMANOFF, C. & HÉRIVAUX, A. La nature du sol et le stationnement des puces (*X. cheopis* et *X astia*). Essai d'interprétation. [**The Nature of the Soil and the Habitat of Fleas.**] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 3/4, 293–300. [12 refs.]

It is well known that fleas may survive in rat burrows under conditions which, as judged by the general climatic conditions, should have proved lethal. That is easily explained by the fact that climatic conditions inside sheltered places, burrows, cracks and crevices are not the same as those outside. This has led the authors to plead that in the ecology of insects there is a distinction between ecoclimate, a summation complex of meteorological factors, and the "microclimate" which may determine the prevalence or preponderance of a flea-species. The same distinction is to be found in the use of terms like site and "micro-site". In this study two closely allied species of fleas are contrasted, *X. cheopis* and *X. astia*. The soils or dust and refuse, which experience had shown could be called *cheopis* soils and *astia* soils were analysed and showed a well marked difference. *Cheopis* soil was sandy clay, impermeable to or retentive of water, while *astia* soil was purely sandy. Chemical analysis naturally showed the former to have a high content of colloidal alumina and the latter to have more colloidal silica. Little difference between the *p*H of the two soils was demonstrable—5·05 : 5·39.

An old observation of Hirst had emphasized the difference in temperature requirements for the habitat of the two flea species, lower for *X. cheopis* than for *X. astia*. The question arose therefore whether the chemical characters of *cheopis* and *astia* soils were simply physical and not nutritional requirements, not even a matter of humidity *per se*, but the physical fact that evaporation of water leads to lowering of temperature. This seems to be the opinion, not absolute of course, of the authors themselves. *W. F. Harvey*

HOPKINS, G. H. E. **Rats, Fleas and Plagues in Uganda.** 54 mimeographed pp., 22 tables & 2 folding maps. [23 refs.] Published by permission of the Director of Medical Services, Uganda. [Undated].

The text of this report, called a reconnaissance report by the author, may be read with pleasure in its entirety. It is permeated throughout by *scepsis scientifica*, by argument on spurious correlations and by the production again and again of the "negative instance". Nevertheless sharp, crisp well-argued conclusions are drawn from experience, reading and the data available. Uganda is bounded on the north by the Sudan, on the west by Belgian Congo, on the south by

Tanganyika and on the east by Kenya. Kenya blames Uganda for all cataclysmic happenings, except drought and earthquakes. Uganda is an upland country with a snow-covered mountain Ruwenzori (16,794 ft.) descending to L. Albert (2,030 ft.), contains the lakes Victoria, Edward and Albert, and the Albert and Victoria Nile rivers. Two excellent maps accompany the report.

The author's work on plague, plague rodents and plague fleas may truthfully be set down as pioneer investigation, for the previous surveys of Uganda had reference to tsetse-fly disease and sleeping sickness. Many of the early data are erroneous, and cerebrospinal meningitis has been mixed up with plague in African diagnosis. His deductions lead him to the view that plague has existed in Uganda from ancient times, perhaps since 542 B.C., smouldering, latent but never absent. This view of the antiquity of plague in a country, though not "autochthonous", reminds one of the existence of plague in India before the arrival of pandemic plague from Hong Kong to reinforce a negligible smouldering rat enzootic. The subject is well treated by Hankin and was specially investigated in the Kumaon Hills by Walton and Stewart Douglas of the Royal Indian Plague Commission of 1898. But to return to Uganda. There is no sylvatic plague in Uganda and the author throws out a warning that a field rodent dead of apparent plague must be certified as a death due to *P. pestis* and not some other *Pasteurella*, also that it is a vector, not a victim, of plague. Two invasions are mentioned of Uganda, one of the mammalian vector *Rattus rattus* replacing (1901–1906) an equally good plague vector *Rattus* (*mastomys*) *coucha ugandae*, and of *Xenopsylla cheopis*. The flea invasion however seems to have been earlier and to some extent independent of its chief host *Rattus rattus*. Nevertheless it is not *X. cheopis* that is the prime plague flea of Uganda, but *X. brasiliensis* which is given as the "normal initiator of all plague-outbreaks in Uganda and in many areas in Kenya". *Xenopsylla bantorum*, a close relation, was presumably the predecessor of *X. cheopis*.

To conclude: "when plague occurs in Uganda at the present day, four factors are invariably present, these being (1) presence of *Rattus rattus* (or in the past *R. coucha*), (2) presence of a sufficiently large population of *Xenopsylla brasiliensis* or *X. cheopis*, (3) presence of *Pasteurella pestis*, and (4) an average rainfall not below about 45 inches. For an epidemic to occur a fifth factor, intimate contact between rats and man, is required". A distinction is to be drawn between "huts" and permanent buildings and between corrugated iron roofs and thatch as regards rat infestation. The invading rat *Rattus rattus*, which is not a burrower and prefers to nest in thatch, still finds ample opportunity to nest in the hut with a kerosene-tin or iron roof, or in burrows already prepared by *R. coucha*. *W. F. Harvey*

HUANG, C. H., HUANG, C. Y., CHU, L. W. & HUANG, T. F. **Pneumonic Plague. A Report of Recovery in a Proved Case and a Note on Sulfadiazine Prophylaxis.** *Amer. J. Trop. Med.* 1948, May, v. 28, No. 3, 361–71, 3 figs. [30 refs.]

Reports of recovery from pneumonic plague are becoming frequent and, if not recovery, unusual prolongation of life. Few of the cases are uncomplicated as regards therapy. The salient points in the present instance are these :—

A case of pneumonic plague, proved morphologically, culturally and experimentally; presumably contracted in the laboratory, by a man of 33 years; commencement of symptoms Feb. 11, 1947; subsidence of fever on Mar. 3, but resolution delayed; "up and around" since May 7; sputum bloody, sometimes red, sometimes of tomato-sauce tint; complication of malaria on Mar. 17, due to blood transfusion; sulphadiazine was started within 48 hours and amounted to a total of 97 gm. between Feb. 13 and Mar. 3, when it was

stopped, because the white cell count had dropped to 3,200/cmm. ; streptomycin therapy about 72 hours after onset, of which the first intramuscular injection was 100,000 units with similar rather small doses every 3 hours. The dose was later increased to 2–3 million units a day ; between Feb. 22 and Mar. 4 about one million units of penicillin were also given for secondary infections ; during treatment 2 blood transfusions, 2 plasma transfusions and 6 intravenous infusions of 5 per cent. glucose were given ; oxygen inhalation was given as required and 10·2 gm. quinine sulphate for malaria ; the plague bacillus isolated on Feb. 14 was sensitive to both streptomycin and sulphadiazine, that of Feb. 26 was resistant to streptomycin, but sensitive to sulphadiazine ; the patient had had 2 injections of Haffkine Institute plague vaccine in 1942 and another in China in Dec. 1943.

Contacts, 3 of them close, and 15 in all, none of whom had been prophylactically vaccinated, received 3 to 6 gm. sulphadiazine daily for adults and proportional doses to children, for one week by the mouth. None of them developed the disease.

One of the conclusions drawn is that sulphadiazine and streptomycin may be more efficacious when used in synergistic combination.

W. F. Harvey

MEYER, K. F., QUAN, S. F. & LARSON, A. **Prophylactic Immunization and Specific Therapy of Experimental Pneumonic Plague.** *Amer. Rev. Tuberculosis.* 1948, Apr., v. 57, No. 4, 312–21, 1 fig. & 5 charts.

In this short article the authors present experimental methods, histological confirmation and sharp conclusions, which should attract the attention of workers in other organismal infections than plague, where animals are also susceptible with man. The therapy is both prophylactic and curative.

No evidence exists that there is a variety of *P. pestis* which is pneumotropic, and the bacteria isolated from bubonic and pneumonic plague are identical. The animals used in these experiments were guineapigs and mice, which are in some respects contrasted animals in their reactions to the plague bacillus, or rather to the plague toxin. A survival rate of only 21 to 25 per cent. in mice after intranasal infection is contrasted with a rate of 80 per cent. in guineapigs, the inequality being attributed in part at least " to differences of susceptibility to plague toxin ". A careful histological examination, so rare in well-established bacterial diseases, shows the course of the infection after intranasal instillation of highly virulent plague bacilli in animals anaesthetized with barbiturate (" 4 to 8,000 organisms per 0·05 cc. per mouse and 0·3 cc. for guineapigs ") :— In 5 to 10 minutes one-tenth of the administered bacilli have reached the deeper respiratory passages. Rapid increase of the bacilli is demonstrable in the lungs, so that by the 48th hour 20 to 500 million " may be cultured from the entire mouse lung. At this stage the blood stream is invaded . . . Guineapigs as a rule are not visibly ill for the first two days but die suddenly between the third and fifth day ".

The conclusions will fully reveal the importance of this work :—" (1) Intranasal instillation of . . . highly virulent plague bacilli produces in mice, guineapigs and cotton rats a primary pneumonia which is anatomically indistinguishable from that observed in man. (2) Active immunization with avirulent strains of *P. pestis* or chemically killed plague bacilli in the form of particulate antigens confers on mice a definite and on guineapigs a marked protection against an intranasal challege infection. (3) Concentrated antiplague rabbit sera possess prophylactic and to a slight degree curative values in pneumonic plague. (4) Sulphonamides are not very effective ", though " when combined with antiplague serum, their therapeutic value, definite in bubonic plague, is

equally demonstrable in the pneumonic type. (5) Streptomycin is thus far the most effective therapeutic agent known for the treatment of plague infections, both bubonic and pneumonic. Over 90 per cent. of experimentally infected mice, when in the septicemic state of lobular plague pneumonia, may be cured with 5 mg. of streptomycin. It is recommended that human pneumonic plague be treated early in the course of infection with daily doses of 4 to 6 g. of streptomycin and that treatment should continue for not less than six to ten days". *W. F. Harvey*

BARNETT, S. A. **Rat Control in a Plague Outbreak in Malta.** *J. Hygiene.* 1948, Mar., v. 46, No. 1, 10–18, 1 map, 2 text figs. & 4 figs. on 2 pls. [17 refs.]

A straightforward clear account is given by the author of an anti-rat campaign in Malta. The rat is the agent in development of plague and the flea-borne endemic murine typhus in the island. In Malta the rat problem was that of a densely populated subtropical area, but not wholly urban for the country is intensively cultivated. Human plague had made its appearance on June 17. Altogether in the course of a year, since when there have been no further human infections, there were 80 cases with 22 deaths. During this year 22,902 rats were examined, 659 being *R. rattus*. Only 20 rats were diagnosed as plague-infected and of these 15 were *R. norvegicus*. It is *R. norvegicus* that is the common rat in Malta and it evidently "played an important part in carrying plague". Reliance was placed for reduction of the rat population on poisoning by zinc phosphide, arsenious oxide, red squill and alphanaphthylthiourea (ANTU). "The method was prebaiting, followed by poisoning with baits and poisons of known efficacy and change of both bait and poison for follow-up treatments". *W. F. Harvey*

CHOLERA

IN DER BEECK, M. Die Epidemiologie der Cholera in Frankreich. [**The Epidemiology of Cholera in France.**] *Ztschr. f. Hyg. u. Infektionskr.* 1948, Apr. 1, v. 127, Nos. 6/8, 526–34.

A historical study.

WAHID, A. A. **A Short Note on Contacts of Cholera at Embaba Fever Hospital.** *J. Roy. Egyptian Med. Ass.* 1948, June, v. 31, No. 6, 487–8.

The author examined from one to three or more swabs each from 600 contacts of cholera during the epidemic of 1947. Positive stools were found in 16 persons without symptoms and it is stated that 12 of these were carriers for only two days. The longest duration of the carrier state found was 7 days. Only 3 of the contacts showed evidence of the disease. No dramatic effect of sulphonamide prophylaxis on the carrier state was observed, nor did this state appear to be related to cholera vaccination or its absence. Two cases showed a latent period of 5 and 6 days, with negative stools, between the day of isolation and the beginning of the carrier state. [This paper is extremely brief; further details of these findings would be desirable.] *H. J. O'D. Burke-Gaffney*

HASSAN, A. **Differential Diagnosis of Cholera.** *J. Roy. Egyptian Med. Ass.* 1948, June, v. 31, No. 6, 471–8.

Two sentences, the first and the last, will show the scientific approach of the author to clinical cholera, the cholera of the text-books, with its ticketed true

vibrio. These are: "Differentiation of cholera from the clinical point of view is a rather difficult problem" and "Every case of diarrhoea without vomiting should be provisionally suspected as cholera and isolated in the hospital, where the final diagnosis of cholera is either proved or disproved".

Notes on examples of diseases which are mistaken for cholera and which were met with in the hospital at Abbassia form the subject matter of the article. These were: (1) food poisoning. (2) acute metallic poisoning, (*a*) the most important, arsenical poisoning, (*b*) acute mercurial poisoning by mercury chloride taken suicidally. (3) severe types of dysenteries, (*a*) bacillary dysentery, (*b*) amoebic dysentery, (*c*) malarial dysentery, (*d*) bilharzial dysentery, (*e*) ciliate dysentery. [There is no mention of vibrio dysentery, El Tor dysentery, so that presumably it was not met with, or was included with true cholera.] (4) pellagra. (5) tuberculous enteritis. (6) some mild forms of diarrhoea: post-prandial, nervous, gastrogenous or an intestinal carbohydrate dyspepsia. (7) acute appendicitis. (8) Addisonian crises. (9) Graves's disease. (10) summer diarrhoea, "cholera infantum". (11) some others. The author draws attention to uraemia, a terminal feature of cholera, to remark that "uraemia itself due to kidney disease or other factors gives rise to diarrhoea, vomiting, dehydration, and acidosis—a picture very similar to cholera". *W. F. Harvey*

BALIGH, A. **Complications encountered among Cholera Cases treated in Ismailia Isolation Camp.** *J. Roy. Egyptian Med. Ass.* 1948, June, v. 31, No. 6, 468–70.

The commonest complication of cholera encountered by the author was *heart failure*. This occurred in (1) most of those patients dying within 24 hours of admission as a result of sudden changes in the blood and ischaemia, (2) sometimes during treatment with large transfusions given rapidly, (2) occasionally during apparent convalescence as a result of toxaemia and myocarditis. Extra-systoles were quite common at this stage, but corrected equilibrium of the blood soon caused them to disappear. Electrocardiographic examinations confirmed that the heart may be so deranged in severe cholera as to fail at any moment during convalescence. In fact 8 apparently well patients did die suddenly at this stage in 10 to 20 days from the onset of the disease.

Persistent suppression of urine and uraemia caused many of the early deaths before lines of treatment were completely established. It was usually due to dehydration and retention of nitrogenous products.

Abortion and premature labour were constant in those pregnant women who had cholera. Of 7 such, 4 aborted, 2 had premature labour and 1 died during labour at term. All of them died within 2 to 3 days, except 1 who died of pneumonia in 5 days. These abortions were complete and without haemorrhage and were attributed to severe purgation, severe reflex uterine contractions and toxaemia. The author does not recommend any interference in such cases, as the abortions were always completed quickly without it.

Five patients died of *pneumonia* and 2 from *pulmonary oedema*; both of the latter suffered from suppression of urine, but the author adds that "oedema was due to sudden overhydration with saline solution".

During the recovery stage, 3 patients developed *maniacal conditions*; 1 recovered completely and the other two died.

Parotitis and *paraplegia* each occurred once and cure was complete in each case.

[The statistical value of this note would have been enhanced by a statement of the total number of cases seen.] *H. J. O'D. Burke-Gaffney*

LAHIRI, S. C. **Sulphadiazine and Sulphaguanidine in Cholera.** *Indian Med. Gaz.* 1948, Jan., v. 83, No. 1, 24–8.

Most of the work on the value of sulphonamides in cholera has gone to show the superior value of sulphaguanidine over the other forms as being non-absorbable and non-toxic. In this study the author uses sulphadiazine, less toxic than sulphathiazole, in the initial dose of 2 gm. followed by 1 gm. 4 times a day as a comparison with sulphaguanidine. Of course in cholera symptomatic treatment is always required to combat dehydration, demineralization and depletion of colloids. Altogether 139 patients received sulphadiazine, 111 sulphaguanidine and 43 pulv. calomel. The result is interesting: "Both sulphaguanidine and sulphadiazine are beneficial in cholera". If children and old men are excluded, the death rate for the intermediate age group, the majority group, is practically the same with both drugs—8·66 per cent. with sulphadiazine and 8·49 per cent. with sulphaguanidine. *W. F. Harvey*

GOHAR, M. A. & ISA, A. A. **Cholera Vaccines.** *J. Trop. Med. & Hyg.* 1948, July, v. 51, No. 7, 144–7.

Gohar has seized the opportunity of the cholera epidemic in Egypt to make useful animal experimentation on vaccines, using the Korein strain itself for this purpose. The animals used were rats and the LD_{50} intraperitoneal dose of the Korein cholera vibrio was 4,000 million organisms. His five vaccines, for each of which 25 rats were provided were: (1) Heat-killed phenol-preserved suspension, at 4,000 million/ml. of which the lethal dose subcutaneously was 4 ml. (2) Formalin-killed, phenol-preserved suspension, of the same strength and having the same lethality as the first. (3) Soluble extract, obtained by adding an equal quantity of normal sodium hydroxide to a suspension at 8,000 million/ml., incubating at 37°C. for a few hours until clear, and neutralizing with HCl to *p*H 7·5. The lethal subcutaneous dose was 3·5 ml. (4) Toxoid obtained by treating the No. 3 toxin with 0·7 per cent. formalin, and incubating at 37°C. for 20 days, by which time it had become non-toxic and the animals immunized with it could resist big doses of toxin. (5) A mixture in equal parts of vaccine and toxoid.

Altogether 6 batches of rats were used, the 6th being the control untreated batch, the test dose the LD_{50}, and the immunizing dosage 2,000 and 4,000 million organisms or equivalent, subcutaneously at a week's interval. The survivals of the 6 batches in the order given were 16, 17, 15, 14, 21, and 11 or, in percentages, 64, 68, 60, 56, 84, 44. "It must be admitted . . . that the number of animals used is too small and the results obtained can only be looked upon as suggestive", in favour of the mixture containing equal parts of both toxoid and vaccine.

An important remark made by the authors, while commenting doubtfully on the distinction between haemodigestion and haemolysis by vibrios, may be recorded: "We found when cultures of the cholera vibrio . . . were kept in the incubator for three days . . . that the clearing was just as intense as that produced by the truly haemolytic El-Tor vibrio; this shows that the difference between the two organisms is more of a quantitative than a qualitative nature. . . ."

The toxoid vaccine mixture takes a long time, by complicated procedure, to prepare and the authors describe "a simple method of preparing an alum-precipitated toxoid vaccine mixture" [see this *Bulletin*, 1948, v. 45, 901].

W. F. Harvey

AMOEBIASIS AND INTESTINAL PROTOZOAL INFECTIONS

SHAFFER, J. G., RYDEN, F. W. & FRYE, W. W. **Studies on the Growth Requirements of *Endamoeba histolytica*. III. The Growth and Multiplication of Two Strains of *E. histolytica* in a Transparent Medium without the Addition of Rice Flour or other Particulate Matter and without Demonstrable Bacterial Growth.** *Amer. J. Hyg.* 1948, May, v. 47, No. 3, 345–50.

The culture of *Entamoeba histolytica* in the absence of bacteria has been attempted for a long time, and these workers have progressed a further step towards the goal. They used a medium consisting of (*a*) the supernatant fluid from a culture of a streptobacillus [this *Bulletin*, 1948, v. 45, 786, 787] in a thioglycollate rice flour medium, (*b*) a bacteria-free filtrate of the specific bacteria complex grown in egg-slope-buffered-saline medium, (*c*) normal horse serum, and (*d*) a low concentration of penicillin.

Amoebae obtained from fresh specimens could not be grown directly in this medium ; they first had to be passed through media containing higher amounts of antibiotics. The culture must be anaerobic and subcultures should be performed every 48 hours (at 37·5°C.). The few streptobacilli present in the cultures either fail to multiply or die out—even after 14 days the medium remains clean. *P. C. C. Garnham*

STEWART, G. T. & JONES, W. R. **The Pathology of an Experimental Amoebic Infection in the Rat.** *Ann. Trop. Med. & Parasit.* 1948, Apr., v. 42, No. 1, 33–45, 5 text figs. & 2 pls. [36 refs.]

By the technique described by JONES [this *Bulletin*, 1947, v. 44, 313] rats were inoculated intracaecally with *E. histolytica*. In different groups, 67–90 per cent. of the animals became infected. The inoculum was 0·2 cc. of the mixed centrifuged deposit of amoebic culture with an equal volume of 10 per cent. gastric mucin. For the study of bacterial action, broth cultures of bacteria were added to the inoculum or were given orally before or after establishment of the amoebic infection. Heavy doses of bacteria ranging from 10 to 1,000 million organisms were administered. In certain experiments, phthalyl sulphathiazole (500 mgm./kgm. orally) or penicillin (500 units subcutaneously) was given four times in the 48–54 hours before or after the operation. After periods ranging from 1 to 14 days the animals were killed and the caeca examined. The infection was judged by the numbers 5 to 0, according to the degree of infection. Heavy infection, ulceration, numerous amoebae, 5 ; inflammation and mucus, numerous amoebae, 4 ; inflammation, many amoebae, 3 ; normal, many amoebae, 2 ; normal, few amoebae, 1 ; normal, no amoebae, 0. For two strains of *E. histolytica* the infectivity and virulence were definitely related, but one strain gave a high percentage of virulent infections unrelated to the infectivity.

The mucosa of the caecum showed evidence of invasion within 24 hours in the shape of minute erosions of the columnar epithelium. Later there was invasion of the villi and crypts by amoebae with some necrosis of the adjacent mucosa. At a later stage the mucosa at the edge of the lesion became heaped up and formed a follicular ulcer containing mucus and amoebae. Beyond the ulcer the mucosa remained healthy. In another type of lesion there was a widespread cellular infiltration by polymorphonuclear leucocytes of the tissues around the original break in the mucosa. There was congestion and focal lymphoid hyperplasia. Amoebae were often scanty. Lesions of this type were especially prevalent when virulent bacteria had been administered in the inoculum. Between these two types of lesion many intermediate forms occurred. At a later stage (3–7 days) the caecum was grossly ulcerated and thickened with

a copious exudation of mucus into the lumen and local peritonitis leading to adhesions. Amoebae were found chiefly in the bases of the ulcers or in the loose exudate, sometimes forming a solid mass. Isolated amoebae were seen in the submucosa and rarely outside the muscularis mucosae. Healing would begin at any time, but usually commenced after seven days. In some cases this was retarded for a few weeks. Death sometimes occurred after 3–4 days but most fatalities were during the first 24 hours and were associated with coliform bacteraemia. No amoebae were observed in the liver.

The lesions were aggravated by the administration of *Bact. coli* and paracolon bacteria. The strain of paracolon remained in the bowel for several days. The administration of penicillin controlled the bacteria and profoundly reduced the severity of the infection. Penicillin was active both prophylactically and therapeutically. Phthalyl sulphathiazole and other sulphonamides were partially effective prophylactically but had no therapeutic effect, though given with penicillin they seemed to increase its activity. The result of the work is that young laboratory rats are susceptible to amoebic infection, the bacterial flora being the major factor in the pathogenesis. With the bacteria controlled by penicillin minimal lesions are produced. In some of the young rats, after the acute infection had subsided, cysts were found in the intestine. In general, the infection resembles that in human beings. *C. M. Wenyon*

GHOSH, N. N., GHOSH, H. & RAY, J. C. **A Preliminary Note on Complement-Fixation Reaction in Amoebiasis.** *Ann. Biochem. & Exper. Med.* Calcutta. 1948, Jan.–Feb., v. 8, Nos. 1/2, 3–10. [21 refs.]

The serological diagnosis of amoebiasis has been re-examined with a view to the preparation of a more satisfactory antigen for the complement deviation test than has previously been devised. An antigen was prepared from cultures of a strain of *E. histolytica* virulent to kittens by spinning down the amoebae in the supernatant fluid of cultures at 1,000 r.p.m. for three minutes. At this speed the major portion of the accompanying bacteria was left in the supernatant fluid, which was discarded. The washed sediment was triturated in sand to a fine paste, and diluted in phenolized distilled water (0·4 per cent. phenol) to nine times its volume. After filtration through filter paper it was stored in the ice chest until required for use. The working dilution of this antigen was 1 in 10, and it was employed with a sheep-cell haemolytic system; the serum under test was inactivated at 55°C. for half an hour and diluted to 1 in 5 before use. Control bacterial antigens were also prepared from the amoeba culture-tubes.

The authors found their antigen more potent and specific than those prepared by alcohol extraction methods. Of 14 persons giving a positive complement deviation test, 7 proved to have intestinal *E. histolytica* infections, and 2 had amoebic liver abscesses. Of 46 persons giving a negative test, 2 were found to harbour *E. histolytica*; both of these were free from symptoms of the infection. [The table setting out these results is somewhat difficult to follow.]

A. R. D. Adams

STEWART, G. T., O'MEARA, P. J. & KERSHAW, W. E. **Observations on Amoebiasis in Ceylon.** *J. Roy. Nav. Med. Serv.* 1948, Jan., v. 34, No. 1, 2–12, 2 figs. [28 refs.]

The sudden increase in amoebiasis at the beginning of 1946 coincided with a fall in the number of cases of undiagnosed diarrhoea and was probably attributable to more systematic methods of investigation. The authors write from their experience at two general hospitals during the war.

Faeces of Asiatic cooks and stewards in three establishments in the different climatic zones of Ceylon were examined by the copper sulphate flotation method. In the low country it was 9 per cent.; at Diyatalawa, up country, 13 per cent.; and in Trincomalee, low country dry zone, 11 per cent. It is to be noted that the percentage of incidence when four specimens were examined was approximately twice as great as when only one was examined. The influence of such a carrier state on the incidence of fresh infections in Europeans exposed to contagion is given in a table which purports to show that the incidence of fresh cases progressively diminished as the food-handlers were effectively supervised. In the majority of instances it seemed likely that constant exposure to infection first occurred in the mess. After a survey in December, 1944, three cooks and eight stewards were found infected with *E. histolytica* and were either treated or transferred to other duties. Thereafter infected food handlers were excluded and this was associated with an abrupt decline of fresh cases. Other means of acquiring infection were eliminated as far as possible. No uncooked fresh vegetables were served and flies were not abundant. A similar fall of incidence occurred in Trincomalee in June 1946 after similar measures had been taken.

Admissions for bacillary dysentery at some periods exceeded those for amoebiasis, and in some a sharp attack of bacillary infection appeared to unmask a latent amoebic infection. But bacillary dysentery rarely caused permanent injury. In this respect amoebiasis was in contrast. Severe cases, complications and relapses were comparatively common and about a quarter relapsed within a few months. The danger of reinfection was high. There were no fatalities among Europeans, but general impairment of health was a serious problem.

The slow onset is shown by a table which indicates that 68 per cent. had been in the station more than six months before the onset of symptoms. The remaining 32 per cent. seem to indicate that signs of infection may develop in less than six months, but for the most part the patients were in good general condition.

In each case diagnosis was made by faeces examination and in a few by rectal scrapings.

The main clinical features are tabulated. Diarrhoea occurred in 84 per cent.; constipation in 10; abdominal discomfort in 81 and tenderness in 59, blood in stools in 49, vomiting in 18 and nausea in 16, loss of weight in 11, pyrexia in 14 and lassitude in 16.

As regards diarrhoea there was a loose precipitate morning stool, but as such an occurrence is frequent in normal individuals, the best pointer for diagnosis seems to lie in recurrent diarrhoea or alteration of the bowel habit.

Sixty-seven cases were dysenteric, but the remainder (73) were diagnosed as amoebiasis from the presence of *E. histolytica* cysts in the faeces.

Severe cachexia and signs of nutritional deficiency were rare and occurred only in patients with relatively long histories of illness.

Plasma protein estimations were performed upon a random sample of 26 patients, of which six showed significant degrees of hypoproteinaemia, each being a severe relapsing case. Lowering of plasma proteins in certain cases has been adduced as evidence of nutritional deficiency in amoebiasis, but it is possible that hypoproteinaemia may be a manifestation of liver damage. Pyrexia was mild and lasted only 24 hours. When persistent and high it was associated with definite signs of hepatitis and once with massive typhlitis.

Sigmoidoscopy.—The classical lesions are not in dispute, but some of the early changes are still ill-defined. Pin-point craters, patchy hyperaemia and localized oedema were observed in cyst passers—changes which were best seen with a magnifying eye-piece.

Raised pin-point yellowish dots with an inflammatory areola were often seen at the recto-sigmoid junction. These scrapings usually yielded vegetative amoebae, but occasionally mucoid material with a few macrophages and leucocytes. A day or two later stool examination or sigmoidoscopic scraping revealed *E. histolytica*.

Six cases of amoebic hepatitis were seen during the period of review. Haemorrhoids and pruritus ani were not uncommon, but the most troublesome complication was post-dysenteric colitis. Apart from *Shigella* infections (bacillary dysentery) the nature of secondary infection still awaits definition. In their experience this occurs only in late and relapsing cases, but clinical evidence is obtained only when the exudate becomes purulent. As regards treatment no original methods are claimed. Emetine injections were given during the dysenteric phase or where hepatitis was suspected, sulphonamides, occasionally with penicillin, where the appearance of frank pus in the stools suggested the presence of heavy secondary infection. EBI, quinoxyl and stovarsol were given for the remainder of the course.

Criteria of cure were : Twelve negative stools for *E. histolytica* and exudate ; sigmoidoscopy : no active lesions ; not more than three bowel movements per day.

The relapse rate between dysenteric and non-dysenteric cases was remarkably similar, which suggests that a patient with dysentery has as good a chance of cure as one passing cysts.

The custom of giving ten or twelve injections of emetine to every case has been to a great extent abandoned, but the authors, on the supposition that vegetative amoebae in lesions of the upper colon become transformed into cysts in the lower colon, suggest that there may be good reason for its continuance in patients without dysenteric symptoms. [See also this *Bulletin*, 1946, v. 43, 557 ; 1947, v. 44, 818.] *P. Manson-Bahr*

HULLSHOFF, A. A. Amoebiasis hepatis. [**Liver Amoebiasis.**] *Nederl. Tijdschr v. Geneesk.* 1948, July 24, v. 92 (iii), No. 30, 2214–20.

PARMER, L. G. **On the Relative Efficacy of Emetine in Intestinal and Hepatic Amebiasis.** *Proc. Soc. Exper. Biol. & Med.* 1948, June, v. 68, No. 2, 362–3.

It is well known that while emetine is effective in amoebic hepatitis and early amoebic abscesses, it is ineffective by itself in amoebic dysentery. This is usually explained on the grounds that the drug is capable of destroying trophozoites, but not cysts of *E. histolytica* ; and since cysts are not usually found in the tissues outside the intestinal lumen, hepatic amoebiasis is more susceptible to emetine treatment, This does not, however, explain why the drug can eradicate trophozoites in the liver ; and although emetine has been used in amoebiasis for more than 35 years, the author observes that the tissue distribution and concentration of this alkaloid have not been reported.

Working in the Pharmacology Section, Research and Graduate School, Army Medical Centre, Washington, D.C., he accordingly injected 24 albino rabbits (2·5 kgm. weight) intramuscularly with 6 mgm./kgm. emetine hydrochloride in aqueous solution. The rabbits were sacrificed in groups of 3 at intervals of 1 hour to 28 days. Pieces of large intestine and liver were analysed for emetine by a method adapted from that of BRODIE, UNDENFRIEND and DILL [this *Bulletin*, 1947, v. 44, 793].

The results for 28 days are shown in a table, which indicates that within an hour the concentration of emetine in the liver was 24·9 mgm./kgm. compared with 5·5 in the intestine. At 12 hours the figures were 41·6 and 1·7 respectively,

and in 4 days 15·4 and 1·2 mgm./kgm. Thereafter the drug continued to be found in the liver in decreasing quantities up to the 28th day, while none was detected in the intestine from the 5th day onwards.

The finding of a high concentration and prolonged presence of emetine in the liver, compared with low concentration and transient presence in the intestine, is put forward as the explanation for the efficacy of the drug in hepatic amoebiasis and its failure in amoebic dysentery in man. [While one hesitates to argue from animal to man in experiments of this nature, the highly significant results of these experiments and their possible implications demand further and extended investigations on this important point.]

H. J. O'D. Burke-Gaffney

DWORK, K. G. **The Use of Para-Aminobenzoic Acid in Amebiasis. Preliminary Report.** *Bull. New York Acad. Med.* 1948, June, v. 24, No. 6, 391–3.

This study was conducted in the Department of Health, New York City, on 12 out-patients with *E. histolytica* infections, all but one of whom were Porto Rican emigrants. As the drug, which is rapidly excreted, was not given at night and no blood levels were done, it was believed that if encouraging results followed, even more favourable results might be expected under hospital conditions. The drug used was the sodium salt of paraaminobenzoic acid (sodium paba).

The dosage of sodium paba employed is not stated in the text, but in a table listing individual results, sodium paba treatment is shown as varying from "2·0 q3h 7 days" to "2·0 q2h 14 days" which presumably means 2 gm. every 3 hours for 7 days to 2 gm. every 2 hours for 14 days.

Nine patients completed the course and four of them had negative stools after 4 to 30 weeks. Of seven patients with symptoms, six showed improvement or disappearance of symptoms after treatment.

It is noted that the non-Porto-Rican case had been refractory to carbarsone therapy, but cleared up with sodium paba.

Another table shows that the successes were obtained in four of the five patients who received the drug at intervals of 2 hours, and that of the five failures four occurred in those treated at intervals of 3 or 4 hours [see also BRACKETT and BLIZNICK, this *Bulletin*, 1948, v. 45, 80].

H. J. O'D. Burke-Gaffney

YOUNG, Viola M. & FELSENFELD, O. **The Occurrence of Intestinal Protozoa in Adults in San Juan, Puerto Rico.** *J. Parasitology.* 1948, June, v. 34, No. 3, 229–30.

The authors refer to previous surveys of intestinal protozoa in Porto Rico by POINDEXTER [this *Bulletin*, 1934, v. 31, 281], FAUST *et al.* (*Puerto Rico J. Pub. Health & Trop. Med.*, 1933, v. 9, 447), and ACOSTA MATIENZO (*ibid.* 1946, v. 21, 369). The difference in scope and methods of these surveys is pointed out, and the authors then describe the present survey designed to ascertain the existing endemicity of intestinal protozoal infections in San Juan and suburbs.

They obtained fresh stools from 600 adult patients, without diarrhoea, in the Presbyterian Hospital of San Juan: the patients in this hospital represented all ages and classes of the general population, but no children were included in this survey. The stools were examined by direct smear and by zinc flotation (Faust).

The results are shown in a table and compared with those of the previous three surveys. It is pointed out that ACOSTA MATIENZO considered her percentages too low, as she only used direct smear. This is reflected in the present survey, where protozoa were found more frequently.

E. histolytica was found in 17·33 per cent. of persons, compared with 12·4 per cent. in Poindexter's survey and 14·5 per cent. in Faust's rural survey 15 years ago. On the other hand, *Giardia intestinalis* (3·83 per cent.) and *Iodamoeba bütschlii* (1·83) were considerably fewer, which may have been due to improved sanitary conditions and to the exclusion of children from the present survey. It was observed that 26·5 per cent. of persons harboured *Endolimax nana*, compared with 16·3 in Faust's survey, which the authors believe may be due to frequent shifts of population from the Continental United States where this parasite is said to be increasing.

Protozoa were found in 57·16 per cent. of the persons examined: two species were found in 14 per cent., three in 8·5 per cent.; and four in 0·5 per cent.

The authors point out that the incidence of *E. histolytica* in symptomless adults has not receded during recent years from the high rates found by FAUST *et al.* Frank clinical amoebiasis is rarely found in the San Juan area, but the present findings indicate that the danger of it persists in Porto Rico. [The date of the paper by FAUST *et al.* is incorrectly given in the list of references as 1943.]

H. J. O'D. Burke-Gaffney

LUIS CARRI, E. Giardiasis intestinal y síndrome convulsivo. [**Intestinal Giardiasis and the Convulsive Syndrome.**] *Prensa Méd. Argentina.* 1948, June 4, v. 35, No. 23, 1094–7.

An account of a case and discussion.

GLAUNER, W. Massive Infektion mit *Isospora hominis* s. *Belli.* [**Massive Infection with** *Isospora hominis.*] *Med. Klin.* 1948, Jan., v. 43, Nos. 1/2, 26.

This note concerns a refugee from Sudetenland who was admitted in August 1946 in a comatose condition. His illness had started suddenly a week before with profuse watery diarrhoea. He was very ill and the condition suggested a diagnosis of typhoid. General and laboratory examinations, including agglutinations, did not provide a diagnosis, but microscopic examination of the stools showed masses of coccidia, of "the type of *Isospora hominis* s. *belli*". In a single microscopic field with the oil immersion lens, 5 to 6 coccidia were seen. A brief description of the parasites is given. The condition resisted sulphonamide therapy but apparently responded to treatment with "Rivanolettes", 2 tablets 3 times daily [1 tablet contains 0·025 gm. of Rivanol] for a week. After 2 days the stools were formed and after 4 the coccidia were no longer detectable in them. Fourteen days after the course of treatment the patient had put on 12 lb. in weight. He has been followed up for a year; no relapses have occurred and he is fit for work.

The author discusses the differential diagnosis of obscure diarrhoeas of this nature, and refers to the uncertain pathology of coccidiosis. It should be kept in mind when one is dealing with sulphonamide-resistant diarrhoeas: the prompt response to "Rivanolettes" in this case was remarkable. [This claim of a severe condition attributed to infection by *Isospora hominis* and of dramatic cure is worthy of more detailed evidence in support of it.]

H. J. O'D. Burke-Gaffney

LAMY, L., MARCHAL, G. & CHEVRIER, A. M. Nouvelles données sur un *Enteromonas* parasite de l'intestin de l'homme. [**Further Notes on an** *Enteromonas* **Parasitic in the Human Intestine.**] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 3/4, 154–8, 2 figs.

Under the name *Enteromonas hervei* n. sp. the authors describe a flagellate which was grown in culture from the faeces of three colonial officers who

suffered from diarrhoea. The flagellate was globular and measured on an average 7 μ in diameter. There was a large nucleus and three long flagella arising from a point near the nucleus. In addition, in the majority of flagellates, a club-shaped process 4 μ in length arose from the body. The flagellate was not found on microscopic examination of the faeces and the authors conclude that it must have been present in the encysted stage which was responsible for the growth in culture. They discuss the nomenclature of the organism and place it in FONSECA's genus *Enteromonas*, though he gave no account of the club-shaped process. Because of the process they place it in a new species as *E. hervei*, but it seems probable that the presence of the process would justify a different genus from *Enteromonas*. *C. M. Wenyon*

LEPROSY

McCOY, G. W. **Leprosy in California—Danger of Infection.** *Pub. Health Rep.* Wash. 1948, May 28, v. 63, No. 22, 705–12.

This is a careful study of the conditions under which leprosy infections occur in the mildly endemic area of California, with an incidence only exceeded in the United States by the defined endemic areas of Louisiana, Florida and Texas. Among 475 cases up to 1940 not more than 14 appear to have been infected in California itself. The main sources of imported infection were, first, China and other Far Eastern countries, and second, the neighbouring endemic areas of Mexico and Louisiana, a very large majority being males. The present inquiry deals for the first time with probable infections within the State, by studying the data accumulated by the health department and the Louisiana state leprosarium. The data were collected by interviewing the patients ; three family group infections were found among those who had lived in California all their lives, seven out of eight of whom had lived with leprous parents ; three were examples of conjugal infections. Among approximately 500 cases inquired into, only 23 appear to have been infected in California itself ; this places the State on a level with Minnesota as a mildly endemic area. It also appears that 8 of the infections occurred in a small area in the middle of the State ; 6 of them were in children infected by their parents, apart from which the likelihood of infection in the area is very small. *L. Rogers*

BRAGA, R. V. Contribuição ao estudo da lepra no meio proletario da cidade do Rio de Janeiro. [**Leprosy among the Poorer Classes in Rio de Janeiro.**] *Rev. Argentina Dermatosifilologia.* 1947, July–Dec., v. 31, Nos. 3/4, 486–92, 7 graphs.

During a period of years (August 1939–47), 66,764 industrial workers were examined in Rio de Janeiro ; 3,006 were suffering from dermatosis of some kind and 231 were infected with leprosy, *i.e.* 0·35 per cent. of the total and 7 per cent. of those with skin lesions. By a series of graphs other details are indicated. The greatest number in any one year was 39 in 1944 and the smallest 20 in 1941, the average being 29 *per annum*. As regards the clinical forms, 93 were of the nerve type, 40 lepromatous and 98 mixed ; 196 of the total were males, 35 were females [but as the respective totals are not given, this has little if any meaning ; all that is stated is " the number of male operatives was greater "] ; 185 were Brazilians, chiefly from Rio, Minas Gerais and São Paulo, 38 Portuguese, and 8 of other nations. Those engaged in work liable to be associated with trauma were the most attacked—stone-masons, metal workers and mechanics. *H. Harold Scott*

STEINIGER, F. Die erbliche Disposition bei der Entstehung der Lepra. **[Predisposition to Leprosy.]** Reprinted from *Ztschr. f. mensch. Vererbungs- u. Konstitutionslehre.* v. 25, No. 2, 245–72 in *Arb. a.d. Reichsgsndhtsamt.* 1941, v. 74, No. 3, 471–98, 15 figs. [Numerous refs.]

This is another long German discussion in support of the speculation of OBERDOERFFER and GEHR that an essential cause of leprosy is poisoning by sapotoxins contained especially in yams. The early part deals with the literature on hereditary infection and hereditary predisposition, from DANIELSSEN and BOECK in 1848 to recent papers by AYCOCK [this *Bulletin*, 1941, v. 38, 21], from which it is concluded that hereditary predisposition is one of the three factors in the causation of leprosy, and another is of course infection by the lepra bacillus. The work of OBERDOERFFER and his German supporters is then examined and the absorption of sapotoxins during the digestion of coco-yams (*Colocasia*) is considered to be the second and central factor, as shown in a diagram of causes of leprosy. This conclusion is arrived at by omitting all reference to the demonstrations by LOWE and CHATTERJI [see this *Bulletin*, 1939, v. 36, 1015] that the German hypothesis is quite contrary to the facts as regards India; the work of DAVEY and ROSS [*ibid.*, 1944, v. 41, 587] which disproved the relationship as regards Nigeria was not published when this paper was written. The paper by CHAUSSINAND abstracted below also shows that it is not applicable to Indo-China. No new facts are brought forward in the present paper of Steiniger, so any who may be interested may be referred to it for his summary of the literature on the subject from the German point of view.

L. Rogers

CHAUSSINAND, R. Contribution à l'étude de la contamination lépreuse. **[Study of Sources of Infection in Leprosy.]** *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 1/2, 17–20.

This inquiry in French Indo-China deals with 1,223 patients of whom 284 acknowledged contact with another such patient, but this is considered to be an under-estimate as Chinese in particular were believed to conceal the truth. The sources of infection were classed as lepromatous in 88 per cent. and nerve cases in 12 per cent. It is also noteworthy that only 45 per cent. of the infected had lived continuously in family contact with earlier cases; 55 per cent. recorded only intermittent contact. The duration of contact is also shown in a table for each group, and it varied between 1 day and 33 years. It is also pointed out that data are wanting to show whether nerve cases with bacillary infection of the nasal mucous membrane are the main sources of the few infections attributable to contact with neural cases. The indications are that leprosy can be contracted through contacts of comparatively short duration. [In another note by the same writer, noticed by title below, it is shown that in 8·83 per cent. of 668 neural cases the nasal mucous membrane was positive for lepra bacilli and the cutaneous lesions were positive in 44 per cent.]

L. Rogers

CHAUSSINAND, R. Examens bactériologiques et leur interprétation dans la lèpre. **[Bacteriological Examinations and their Interpretation in Leprosy.]** *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 1/2, 59–73. [11 refs.]

CONTRERAS, F. & JAQUETI, G. La reacción de Mitsuda en sujetos alejados de ambiente leprógeno. **[The Mitsuda Reaction in Persons away from Leprous Surroundings.]** *Rev. Argentina Dermatosifilologia.* 1947, July–Dec., v. 31, Nos. 3/4, 537–43, 5 figs.

[A paper "giving one furiously to think."] Mitsuda in 1916 published his celebrated reaction and since 1923 knowledge of it has spread; positive results

are obtained in tuberculoid and neural leprosy, negative generally in the lepromatous; subsequently, the early and late reactions in contacts and cohabitants and in children separated from their infected parents were described.

The authors have paid attention rather to its diagnostic than to its prognostic value, since CASTELLO recorded positive reactors among healthy subjects and GOUGEROT and DE BEURMAN positives among those with cutaneous tuberculosis without leprosy, and lastly, FERNANDEZ after vaccination with BCG.

The authors have carried out the test—injecting intradermally on the anterior surface of the forearm 0·1 cc. of the antigen and noting the result after 24, 48 and 72 hours, 7 days and a fortnight, so as to include late reactions as well as early—in 100 persons, 50 women and 50 men, suffering from non-leprotic dermatoses and venereal disease. Forty-four gave a positive reaction, 25 men and 19 women. Those giving the most marked reactions were patients with lupus, "verrucose tuberculosis" and scrofulodermia; next those with varicose ulcers, and some giving "fleeting positives" were cases of syphilis, psoriasis, ecthyma, eczema and alopecia. The reaction was intense and persistent in two patients, one with tertiary syphilis, the other with tabes dorsalis. The authors conclude that, seeing the high percentage of positives (44 per cent.) in subjects free from leprosy, the test is of no diagnostic value in this disease.

H. Harold Scott

CHAUSSINAND, R. La réaction de Mitsuda, indice de l'immunité relative antilepreuse. [**The Mitsuda Reaction as an Index of Relative Immunity to Leprosy.**] *Acta Tropica.* Basle. 1948, v. 5, No. 2, 160–77. [22 refs.]

This paper confirms the prognostic value of the Mitsuda (lepromin) test and also records observations which throw light on the nature of the reaction. It is based on over 1,500 reactions to intradermal injections of lepra bacilli obtained from nodules, with observations after 24 and 48 hours and weekly up to two months. The later ones were graded as +++, ++, or + in accordance with measurements of the nodular infiltration of over 1 cm., 0·5 cm. to 1 cm. and 0·2 to 0·5 cm. in diameter. No positive reactions were obtained in L and LN cases, but neural cases as a whole reacted in 79·9 per cent. and the degrees of the reaction were in inverse proportion to the number of lepra bacilli in the lesions, while decline in the reaction precedes any increase of the organisms. Positive reactions therefore indicate some degree of immunity, and the reaction is of prognostic but not of diagnostic value.

Of greater interest are the data of the reactions of 231 healthy children aged from 1 to 8 years to both tuberculin and to lepromin; for of 142 who were positive to tuberculin no less than 95·1 per cent. were also positive to lepromin; whereas of 89 children negative to tuberculin 80·9 per cent. were also negative to lepromin. Moreover, children negative to both were made susceptible to lepromin through BCG vaccination. Anti-leprosy immunity may thus result from infection with either leprosy or tuberculosis owing to the similarity of the two antigens, and a positive lepromin reaction in a child who is negative to tuberculin may have some diagnostic value. These important observations were confirmed by animal experiments which demonstrated that many animals negative to both tests may be made positive to both by previous injection with tubercle bacilli or BCG, and animals inoculated with lepromes gave positive lepromin reactions after three to four months. Anti-leprous immunity is an acquired relative immunity, which may also show itself after infection with tubercle bacilli (bacterial parallergy). BCG injections may, therefore, conceivably produce some slight resistance to leprosy infections.

L. Rogers

BECHELLI, L. M. Da conveniencia de se fazer a lepromino-reação nos funcionarios que trabalham em contacto direto com o doente de lepra. [**Importance of subjecting Attendants on Lepers to the Lepromin Reaction.**] *Rev. Argentina Dermatosifilologia.* 1947, July–Dec., v. 31, Nos. 3/4, 484–5.

The prognostic value of the lepromin reaction is well known to leprologists; the lepromatous are negative and the tuberculoid positive in the majority of cases and ROTBERG has reported that reactivation of lepromata is common among the lepromin-negative and that positive reactors do not acquire the disease, or, if they do, the evolution is that of the tuberculoid type. Hence the author proposes that the test should be carried out on all who are about to work in direct contact with leprosy patients. Even those who give no history of contact with patients may give a delayed positive. Those working in leprosaria who react positively may continue in their work, but should be watched so that, if they become negative, they may change their occupation and be entitled to favourable consideration of a request for compensation. Observations tend to show that it is rare for healthy officials to contract the disease; seven who have shown symptoms had been in contact with lepers before entering on their duties, and one only gave no such history. But, though the number may be small, there is no doubt that the possible danger exists and it would be foolish to neglect precautionary measures. *H. Harold Scott*

OLMOS CASTRO, N., ARCURI, P. B. & BONATTI, A. A. Reacción, suerológica de floculación en lepra. Su aplicación practica en el diagnóstico y profilaxis. [**The Flocculation Reaction in Leprosy.**] *Rev. Argentina Dermatosifilologia.* 1947, July–Dec., v. 31, Nos. 3/4, 528–31.

CASTRO and BONATTI in 1945 recorded some results with sera of lepra patients and an antigen with lepromata [see this *Bulletin*, 1946, v. 43, 849, 850, where details of the antigen preparation are given]. The authors now report the results of the test in a larger number of cases, 1,816, of whom 224 were suffering from leprosy (162 the lepromatous form, 62 the tuberculoid) and 1,592 either healthy subjects (1,108) or suffering from other diseases, syphilis, pulmonary tuberculosis, parasitic infections (malaria, American trypanosomiasis, leishmaniasis), brucellosis, typhoid, etc., and 106 contacts of leprosy. Of the 162 of the lepromatous group 119 (73·5 per cent.) gave a positive flocculation, only 3 of 62 (4·8 per cent.) of the tuberculoid type; together 122 out of 224 (54·4 per cent.). Of the 1,108 healthy subjects 2 reacted positively; of the 106 contacts 4 (3·7) were positive. Only 10 of the 1,592 "healthy and other diseases patients" gave flocculation; of these, 4, as stated, were living with leprosy patients; 3 gave very strong Kahn positives, 1 had tuberculous cavities in the lungs and died soon afterwards; only 2 were clinically healthy.

H. Harold Scott

KOPACZEWSKI, W. Lactogélification et lèpre. [**Lactogelification and Leprosy.**] *Bull. Inst. Hyg. Maroc.* 1946, v. 6, 41–9. [21 refs.]

SCHUJMAN, S. Influencia benéfica de la reacción leprosa en la evolución de los casos lepromatosos. [**Good Effect of the Leprous Reaction in the Evolution of Lepromatous Cases.**] *Rev. Argentina Dermatosifilologia.* 1947, July–Dec., v. 31, Nos. 3/4, 506–12, 2 figs. English summary.

Ten years ago Dr. de Souza Lima told the author that leprous reactions seemed to be followed by improvement of lepromatous patients and to retard the progress of their disease. The author has now studied this question in 33 patients as regards, first, the cutaneous and, second, the ocular lesions.

Speaking of the skin lesions, 12 of the 33 improved and all had had leprous reactions ; 7 remained stationary and again all had had the reaction ; 14 were worse and of these 4 had had the reaction, 10 had not. Of the 31 with ocular lesions who were studied, 21 had had the reaction and of these in 13 the eye condition had remained stationary and in 8 was worse ; of 10 who had had no such reaction 2 were stationary and 8 were worse. Two cases are recorded in detail illustrating the first of these points, with photographs of the patients showing the changes which took place ; both were L_3 cases.

The author's conclusions differ, therefore, from those of BECHELLI and COSTA VALENTE of São Paulo (*Rev. Brasileira de Leprologia*, 1937, v. 5, Special Number, p. 167) who stated that, though some might improve, the majority became worse after the reactions. *H. Harold Scott*

SCHUJMAN, S. & CASTAÑÉ DECOUD, Anibal. Modificaciones histopatológicas comprobadas en casos lepromatosos beneficiados. (*a*) Con tratamiento chaulmoógrico. (*b*) Con tratamiento promínico. [**Histological Changes in Lepromatous Patients treated with** (*a*) **Chaulmoogra,** (*b*) **Promin.**] *Rev. Argentina Dermatosifilologia*. 1947, July–Dec., v. 31, Nos. 3/4, 502–6, 4 figs. English summary.

The authors treated 30 lepromatous patients with chaulmoogra and 10 with promin. From 7 of the former and 2 of the latter biopsy specimens of the skin were taken, one at the start of the treatment, the other later when there was only a residual lesion. Some had biopsies at intermediate stages. The changes are shown by four microphotographic reproductions and the details of the different parts of the skin section in each of the nine are described in a table. These may be summed up by saying that the infiltration of the dermis is much reduced, the corium is thickened owing to reabsorption of the infiltrated area ; the bacilli are reduced in numbers and broken up ; in some no bacilli can be seen at all. These changes were seen in those treated with either drug, chaulmoogra or promin. *H. Harold Scott*

FIOL, H., JONQUIERES, E. D. L., BRUSCO, C. M., MELAMED, A. J. & FIRPO, C. J. Tratamiento de la lepra con promin (promanida). [**The Treatment of Leprosy with Promin.**] *Rev. Argentina Dermatosifilologia*. 1947, July–Dec., v. 31, Nos. 3/4, 531–7.

The results of treatment by promin of 125 patients suffering with the lepromatous type of leprosy are reported. Forty-three had had less than 6 months' treatment and of these 30 [stated as 69·7 per cent.] were improved, 12 remained the same and one was worse ; of 71 who had had 6–12 months' treatment 47 (66·2 per cent.) were improved and 24 unchanged, none was worse ; of 11 who had had more than one year's treatment 10 were better and one unchanged. Tables are given presenting the results in other ways : First, according to total dosage of the drug. Four had received from 900 to 1,300 gm. and all had improved ; 36 had had 500–900 gm. and of these 28 were better, 7 stationary, and one worse ; of 85 with less than 500 gm. 55 were better and 30 unchanged, none was worse. Another table gives the daily dosage and results. Of 13 receiving up to 1 gm. daily 7 were better, 6 stationary ; of 59 receiving 1–1·9 gm. 38 were better, 20 stationary, one worse ; of 45 receiving 2–2·9 gm. 35 were better, 10 stationary ; 8 received between 3 and 7 gm. daily and 7 improved, one remained unchanged. In 106 the Mitsuda reaction was carried out ; 6 were marked, 4 weak, and 96 negative.

The results would be still better, say the authors, if chaulmoogra were given at the same time and other adjuvant treatment such as liver, vitamins, general tonics and such like. *H. Harold Scott*

FERNÁNDEZ, J. M. M., CARBONI, E. & TOMASSINO, P. Tratamiento de la reacción leprosa mediante transfusión de sangre de convalecientes de reacción. [**Treatment of the Leprous Reaction by Transfusion from Convalescents from the Reaction.**] *Rev. Argentina Dermatosifilologia.* 1947, July–Dec., v. 31, Nos. 3/4, 493–502, 4 figs.

The authors in treating 173 patients with diasone (1·5–3 gm. daily) observed 100 cases of leprous reaction. After enumerating a score or so of treatments which have been suggested from time to time, they record their experiences with blood transfusion. They transfused 60 patients, with 100 to 250 cc. of blood from 32 patients convalescent from a recent attack, 11 at some other period, not convalescing, and 17 healthy subjects. Results were regarded as good if the symptoms improved with crisis between the second and eighth days. Some [? how many] had only a single transfusion, others had several. The blood of convalescents proved much the best. Of 32 receiving the "convalescent blood" 22 were greatly benefited and 7 others gave good results, and there were three failures; of 11 given "non-convalescent blood", the results were very good in 2, good in 3, failures in 6; of 17 transfused with healthy blood 5 results were very good, 6 good, 6 failures.

[Other information is presented in tables which, however, are so poorly reproduced that they are entirely illegible even with the help of a lens.]

H. Harold Scott

DAVEY, T. F. **The Treatment of Leprosy with Sulphetrone.** *Leprosy Review.* 1948, Apr., v. 19, No. 2, 55–61.

This is a preliminary report on a trial of a new sulphone drug (sulphetrone) for over five months in 17 lepromatous cases, all advanced ones except two macular cases. Hydnocarpus oil had previously been used for long, but 7 of the cases were advancing rapidly and the remainder had been more or less stationary for some time. Tablets of 0·5 gm. were given, commencing with one a week and working up gradually to 3 gm. daily on six days of the week according to tolerance. Ferrous sulphate was given during rest periods of two weeks following six weeks of treatment. In all the patients the haemoglobin remained at about 60 per cent. and the drug proved to be relatively non-toxic. The results show that no patient became worse, in 2 little change occurred but the rest showed notable improvement which was very marked in 7 cases, and entirely transformed the outlook. Bacteriological improvement has not equalled clinical advances, but two have become negative and the bacilli have been reduced in nine others. In subsiding lesions, degenerating forms of bacilli are more numerous. Moreover, in 11 of the 17 cases the lepromin reaction has changed from negative to positive. The new drug promises well.

L. Rogers

CHAUSSINAND, R. A propos de l'action des sapotoxines d'origine alimentaire sur l'infection lépreuse. [**The Action of Sapotoxins of Alimentary Origin on Leprosy Infection.**] *Bull. Soc. Path. Exot.* 1947, v. 40, Nos. 11/12, 424–7. [10 refs.]

In this paper the hypothesis of the German writers, OBERDOERFFER and GEHR, that the consumption of yams containing sapotoxins predisposes to leprosy, is put to the test and found wanting in the case of Cochin-China, where *Colocasia esculenta* is widespread. It is gathered during November and December, but forms only a small part of the diet because it is costly. Animal experiments by the author show that the addition of 100 gm. of yams a week to a normal diet of guineapigs exerted no poisonous effect although an exclusive

diet of yam was highly toxic. Inquiries show that in Cochin-China yams form only a small part of the indigenous diet, and that the poor, who suffer most from leprosy, rarely eat any yam on account of its cost. Of 14 white leprous patients, only 2 had ever eaten yams. Examinations of cases for any seasonal increase of lepra bacilli showed such an increase in April to September, that is before the yam season. The claim that feeding animals on yam makes them more susceptible to inoculated leprous tissues was not confirmed. The hypothesis of the German writers thus receives no confirmation [and the author in this agrees with many other investigators]. *L. Rogers*

FERNÁNDEZ, J. M. M. & BERGEL, M. Una doctrina terapeutica basada en los procesos de oxidorreducción. Su aplicación en el tratamiento de la lepra. [**Treatment of Leprosy by Oxygen-reduction.**] *Rev. Argentina Dermatosifilologia.* 1947, July–Dec., v. 31, Nos. 3/4, 513–27, 7 figs. [25 refs.] English summary.

The main principle of chemotherapy is the employment of a drug which is fatal to the causative organism but well tolerated by the body ; in other words, a substance with marked parasitotropic but minimal organotropic action. Reduction of oxygen is a vital process of all living things and oxygen is necessary for the life of *Myco. tuberculosis* and *Myco. leprae*, as is clear from the work of Soule and McKinley, Rich, Grau Triana, Loebel and others.

Diasone has been, and is, used successfully in the treatment of leprosy, yet is not directly bactericidal or bacteriostatic ; it acts by reducing the blood-oxygen. One of the constituents of diasone is metanal [formaldehyde] sulphoxylate of sodium, M.S.S. (known commercially as Rongalita C) which contains two powerful reducing chemicals ; formaldehyde (19·48 per cent.) and hyposulphite of sodium (56·49 per cent.) and has the formula CH_2-OH-SO_2Na, $2H_2O$. The product used medicinally contains 96·98 per cent. of M.S.S. and is used in 10 per cent. solution in doubly distilled water, injected intravenously within 48 hours of preparation. If taken by mouth it is badly absorbed and causes purging ; intramuscularly it causes much pain. It is injected in doses of 20 cc. (2 gm. M.S.S.) every 8 hours, or 30 cc. every 12 hours, in a course of 15–30 days, then an interval of 5–7 days. It is well tolerated in even high doses (20 and even 40 gm. have been given in cases of mercury poisoning), but the vein tends to become sclerosed. The only signs of intolerance are transitory nausea, some diarrhoea and diuresis.

Twelve cases of leprosy have been thus treated by the authors, all adults, 8 women, 4 men, and all of the type L_2. Brief details are given of four patients. Nodules were observed to soften, local reaction was never alarming or sufficiently severe to interrupt treatment, bacteria lessened in number, became more granular and lost their acid-fast property. In three patients a temporary stoppage of treatment was necessitated by a sharp leprous reaction which, however, was of brief duration. *H. Harold Scott*

ROTBERG, A. Novas perspetivas no terreno da profilaxia da lepra. [**Recent Views on Leprosy Prophylaxis.**] *Rev. Argentina Dermatosifilologia.* 1947, July–Dec., v. 31, Nos. 3/4, 474–84.

The author discusses immunological reactions, the Mitsuda test, the value of the Lepromin reaction, treatment, segregation and discharge briefly and in general terms, and states as his conclusion that the fundamental basis of prophylaxis is isolation [segregation ?] of the infective patient and his treatment, examination of all close contacts and out-patient treatment of the non-infectious, that those with cutaneous lesions revealing bacilli, but with nasal mucus negative, should attend at the dispensary, those Mitsuda-negative being under more

strict control than the positive and more energetically treated. When the nasal mucus becomes positive the patient should be interned without delay. Great caution should be exercised in releasing interned patients on parole, permission to go about depending on steadily improving clinical condition, disappearance of organisms from the lesions and the possibility of control outside. Tuberculoid patients may be kept at home, or taken into hospital if necessary until the nasal smears are negative and the more obvious lesions subside. Lastly, all contacts should have a Mitsuda reaction carried out ; those positive should have the privilege of visiting those interned and their friends, while the negative should attend weekly for examination. *H. Harold Scott*

BECHELLI, L. M. Posição dos doentes de forma tuberculoide incaracteristica (inflamatoria simples) na profilaxia da lepra. [**Status of Tuberculoid Leprosy Patients in Prophylaxis of the Disease.**] *Rev. Argentina Dermatosifilologia.* 1947, July–Dec., v. 31, Nos. 3/4, 468–74.

This is one of a series of papers presented at the 4th anniversary of the Founding of the Argentine Association of Dermatology and Syphilology. The author pleads for less rigorous treatment of those suffering from the tuberculoid or " non-characteristic, non-inflammatory " form of leprosy. The prevailing idea among doctors in general and the public is that " leprosy is leprosy " and any patient so diagnosed is a menace and should be suspect if not isolated. He shows that this view is unjust to the patient and burdensome to the State and thinks that they should be allowed to go free, live with their families and carry on their occupations (with certain restrictions), under observation but unmolested so long as they remain bacteriologically negative. The actual number of lesions present has no bearing on the case. Naturally, if the condition becomes clinically worse and bacterial examination reveals the presence of *Myco. leprae*, observation should be more strict and examination more frequent. Later, improvement may take place and the lesions become free from bacteria, but if the condition continues to deteriorate the patient passes from his former category and segregation and active treatment are called for. In cases " under observation " the lepromin reaction should be carried out from time to time. Furthermore, attention should be paid not only to the patient himself, but also to his contacts and associates ; though he himself is a " burnt out " case or non-infective, contacts, family or other, may be positive.

H. Harold Scott

MACDONALD, A. B. **Rehabilitation—the Industrial and Social Work of a Leper Colony.** *Leprosy Review.* 1948, Apr., v. 19, No. 2, 45–55.

This is an interesting account of 19 years of remarkable work in combating leprosy at Itu in Southern Nigeria, during which an agricultural colony of 3,500 resident patients has been built up, with five villages, hospitals, babies' home, school, workshop, roads, a canal for transporting agricultural produce, court, market, farms, etc. Medical, educational, industrial, agricultural, social and religious work is carried on—all as a result of the efforts of Dr. Macdonald and his able wife. This article should be read in the original by leprosy workers.

L. Rogers

CHORINE, V. & CROUGUE, O., Mlle. Un seul bacille de Stefansky peut infecter le rat. [**Infection of a Rat by a Single Stefansky Bacillus.**] *Bull. Soc. Path. Exot.* 1947, v. 40, Nos. 11/12, 421–4.

HELMINTHIASIS

GAUD, J., FAURÉ & SOLÉ. Variations dans le temps des index d'infestation humaine dans la bilharziose vésicale marocaine. [**Temporary Variations in the Indices of** *S. haematobium* **Infection in Morocco.**] *Bull. Inst. Hyg. Maroc.* 1946, v. 6, 55–60. [10 refs.]

Schistosomiasis is usually considered to be an endemic disease, not subject to great fluctuations in incidence, but the authors, as a result of investigations made in Morocco during the period 1940–44, have revised their views in this matter. They quote, for 4 foci of *S. haematobium* infection, the findings of previous investigators, and their own more recent figures, and show that in most of the villages the recent figures are much lower than the earlier figures. In the more recent investigations, moreover, *Bulinus* snails were not easily found. [In one of the tables only the percentages of positive findings are recorded, and in some of the villages the number of persons examined is small, so that the incidence rate as calculated must be subject to very large chance of error ; nevertheless, the total figures are big enough to justify the opinion that there has been a considerable reduction in incidence.]

They discuss the possible reasons for these differences, which may be as much as 10 to 1 and are usually 3 to 1. Differences in technique are not probable, and treatment cannot account for the change, because in some of the areas it was not given. There may be a seasonal factor, and the examinations were not always made at the same time of the year, but it is unlikely to be important. It seems as if *S. haematobium* infection behaves as an epidemic disease, and that when human infection is comparatively rare the adult infection rate is higher than the childhood rate, and the snails are scanty. The disease is relatively benign in Morocco. *Charles Wilcocks*

SCHWETZ, J. Sur l'état sanitaire de la région du Lubilash et tout spécialement sur la bilharziose dans cette région. Rapport sur une reconnaissance effectuée en janvier-février 1946. [**Health Conditions in the Region of Lubilash (Belgian Congo), especially as regards Schistosomiasis : a Survey made in January-February 1946.**] *Inst. Roy. Colonial Belge. Bull. des Séances.* 1947, v. 18, No. 2, 519–77, 3 maps & 11 figs. on 2 pls.

[The river Lubilash lies towards the southern part of the Belgian Congo. In this report the author gives not only the results of examinations of the people carried out by himself and his colleagues, but also the results of work done during the past few years by resident medical auxiliaries who have examined large numbers of people in their own areas. Although *Schistosoma mansoni* is not referred to by name, the whole account is concerned with the results of examinations of faeces, and, no doubt, that is the worm in question. The surveys and examinations here recorded, in spite of the limitations admitted by the author, give an impression of the prevalence of schistosomiasis which could not be so accurately conveyed by figures derived from hospital practice. They show that intestinal schistosomiasis is widespread over the whole area.]

The author remarks that although schistosome eggs are often found in routine examination of the faeces of persons who have no symptoms, it would be unwise to ignore them because the infection can lead to serious and even fatal illness. In 1939 he found that about 50 per cent. of the people living on the shores of Lake Albert were infected. In 1945, on his return to the Congo, he learned that the disease was prevalent in the Lubilash area, and was requested to investigate it. In this region there was one medical man (at Katanda), and there were three medical auxiliaries in the countryside. All were working independently of each other. The infection has existed in these parts for at least 15 years,

according to reports, and a sanitary inspector of the area drew attention to it in 1942, and about the same time the cotton companies of the area noted a heavy mortality due to the condition known locally as *ditoka*, thought to be schistosomiasis.

Snails of various genera were found in the numerous streams of the country; the most common were of the genera *Planorbis*, *Limnaea*, *Lanistes*, *Pyrgophysa* and *Physopsis*. The species of *Planorbis* were *P.* (*Biomphalaria*) *adowensis* or *P.* (*Afroplanorbis*) *salinarum*, and in one place the large *P.* (*Afroplanorbis*) *tanganikanus* was taken [see also this *Bulletin*, 1947, v. 44, 825].

The author digresses from his main theme to discuss *ditoka*, which is probably the same as the *diboba* or *nzadi* described by PIERAERTS [see this *Bulletin*, 1942, v. 39, 99; 1947, v. 44, 225], and is characterized by depigmentation of skin and hair, anaemia and oedema. It is a disease of the very poor and is probably associated with severe malnutrition and hookworm infestation, but the name may be applied by the Africans to a variety of severe chronic illnesses, and schistosomiasis is probably a factor in some cases.

In a table the author summarizes the findings of the three medical auxiliaries during the years 1943–45, when some 172,000 persons were examined. In 1943 the rate was 29·8 per cent., and in the two succeeding years 15·7 and 15·8 per cent. respectively.

He remarks that the true incidence must be higher, probably much higher, than this because as a rule only one specimen was taken from each person, and concentration methods were not used. In one area the reported figure was 69 per cent., and there were considerable differences between the rates in different places. As a rule the rates in adults were considerably higher than in children. Hookworm infestation was present in 26·6 per cent. of those examined in one large area. In certain places on the edges of the Lubilash area the incidence of schistosomiasis was much lower, below 2 per cent.

The author's team, which included Dr. MUYNCK, a medical auxiliary and 5 microscopists, made a survey of 1,629 people in 9 places, examining one specimen from each person; the incidence of intestinal schistosomiasis ranged from 1·4 to 14·9 per cent. (except in one district of 50 per cent.), and of hookworm from 36 to 66 per cent. In general the infections were fairly light.

Of other diseases, pulmonary tuberculosis is the most serious; it is not, perhaps, very common, but persons with positive sputum are reported regularly by medical men in the neighbourhood. Trypanosomiasis was found in 0·62 per cent. of over 100,000 examined during 1946 (not by the author), but in one village 15 per cent. of the inhabitants were new cases. Leprosy and syphilis occur, and also onchocerciasis with blindness.

There are 10 dispensaries, some built by the cotton companies, some by the government and one by a mission.

In a final note the author makes the point that schistosomiasis is a disease of cultivators, that up to 50 per cent. of the people are infected in some places, but that the infection is usually light. He remarks that in studying the Africans it is necessary to go to their own villages, since if the people are required to travel far to an examination centre, the very sick cannot do so, and some others will not. He suggests that an autonomous medical mission should be formed to study and deal with these remote people, and to examine them all in their own places, and that it should consist of 4 medical men and 6 auxiliaries [the precise status of whom is not given; they are probably Europeans]. For the hospital and laboratory needed for such a mission an initial sum of 3,000,000 francs and the annual sum of the same amount would be necessary. In a postscript he states that the government agrees with his suggestion but that the government organizations will probably carry out the work.

Charles Wilcocks

FERRO-LUZZI, G. Studio sulla bilarziosi intestinale da *Schistosoma mansoni* in Eritrea. [*Schistosoma mansoni* **Infection in Eritrea.**] *Boll. Soc. Ital. di Med. e Igiene Trop.* (Sez. Eritrea). 1948, v. 8, Nos. 1/2, 5–18, 2 figs. [12 refs.] English summary.

The first case of infestation by *Schistosoma mansoni* in Eritrea was reported by SATTA in 1934 [this *Bulletin*, 1936, v. 33, 553 ; 953] ; the second by DIENA in 1935. Now, the disease is endemic in several places in Eritrea, notably in villages around Asmara, Saganeiti and Adi Ugri. The author names several of these. Five species of molluscs were identified there, *viz. Planorbis abyssinicus, P. rupellii, Limnaea raffrayi, L. africana* and *Bulinus raymondianus*. The first two of these were found naturally infested. Their biological characters, their reaction to temperature, their resistance to drying, etc. are noted. Two photographs illustrate a highly infested zone, near Szo'olot. Children accompany animals to the streams and adults wash and bathe in them and infestation takes place *via* the skin and by ingestion. Preventive measures follow the usual lines : destruction of vector molluscs, careful supervision of disposal of excreta, education to drive home the ways of infestation, the dangers of infestation of and by water, and, lastly, the treatment of patients.

H. Harold Scott

RAPER, A. B. **Cerebral Schistosomiasis.** [Correspondence.] *East African Med. J.* 1948, June, v. 25, No. 6, 262–3.

The author refers to the suggestion made by GELFAND [this *Bulletin*, 1948, v. 45, 721] that some cases of epilepsy appearing in adult Africans may be due to cerebral schistosomiasis. He quotes the literature to show that the two African species of *Schistosoma* are less inclined to invade the brain than is the Oriental species ; and in fact the literature of cerebral schistosomiasis appears to indicate that " up to the present *S. japonicum* holds the field as the sole proved invader of the brain " [for a full discussion of ectopic lesions in schistosomiasis, see FAUST, this *Bulletin*, 1948, v. 45, 716 ; in his original paper, Faust quotes 56 cerebral lesions, of which 4 are attributed to *S. haematobium* and 8 to *S. mansoni*, but only one of these, a *mansoni* infection, was confirmed pathologically ; this was a case reported personally to Faust by Carrera in Porto Rico].

The fact that such recorded schistosome infections of the brain other than those by *S. japonicum* appear to be lacking in Africa is attributed by the present author to the possibility that sufficient search has not been made for them ; and he suggests that a large scale investigation in an endemic area would almost certainly be rewarded.

He then records a case of an African soldier who was brought in dead to hospital in 1942. There were many flukes in the liver and petechiae on the pericardium and peritoneum. The brain and meninges were congested, but there was no evidence of meningitis or malaria. There was what appeared to be a diffuse capillary haemorrhage in the pons, but histologically no extravasation of blood was seen ; the capillaries and venules were blocked by thrombus and digestion of the brain-tissue showed *S. mansoni* eggs. A digest of the liver showed *mansoni* and *haematobium* eggs. While the characteristic granuloma surrounding ova in the brain was not present, it is likely that the man died from vascular blockage by an adult fluke or by ova. This is claimed as the first recorded case in which *S. mansoni* ova were found in the brain. The author adds that in seven other attempts to find ova by digestion in different brains the results were negative.

He also quotes a case of another African soldier, with a diagnosis of extra-medullary tumour. No ova were found in the excreta and there was no

eosinophilia. Laminectomy revealed the presence of a dense plaque of fibrous tissue compressing the cord: removal resulted in complete recovery. Section showed that the fibrous tissue had been laid down around an adult fluke: calcification was considerable, so that the species could not be identified. Two years previously the patient had first experienced pain in the legs and difficulty in walking; later a spastic paralysis had developed. It is suggested that the initial acute lesion had corresponded with the arrival of the adult worm in the spinal canal. *H. J. O'D. Burke-Gaffney*

WATSON, J. M., ABDEL AZIM, M. & HALAWANI, A. **Investigations on the Antibilharzial Action of Miracil D (Nilodin).** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1948, July, v. 42, No. 1, 37–54, 1 pl. [29 refs.]

Miracil D is a new drug for the treatment of schistosomiasis. It is 1-methyl-4-diethylaminoethylaminothioxanthone hydrochloride [see this *Bulletin*, 1948, v. 45, 526].

In patients treated in Egypt toxic effects (if present) were slight and transient. The commonest were anorexia, nausea and vomiting. In a few cases vertigo, tremors, and tinnitus occurred. Heart, liver and kidney functions, and blood pressure were normal. There were no significant changes in the blood apart from some increase of eosinophilia. A few patients showed idiosyncrasy marked by lassitude, restlessness, insomnia, nausea, metallic taste, tingling of the skin, headache and lumbar pain.

Experiments were first carried out on mice, and gerbils infected with *S. mansoni*. The results obtained [for which the original paper should be consulted] confirmed Kikuth's reports. To kill all the worms it was necessary to give six daily doses of 40 mgm. per kgm.

The first group of 20 patients contained 14 *S. haematobium* infections, 2 *mansoni* infections and 4 double ones. They were given 2 doses of 0·4 gm. (7–10 mgm. per kgm.) with an interval of 3 days, and they were observed for 42–67 days. Four of the 6 *mansoni* infections and three of the 18 *haematobium* ones seemed to have been cured.

The second group contained 12 patients, infected with *S. haematobium*, who were given 3 doses of 0·4 gm. [stated per kgm. but presumably per person] at intervals of 3 days. They were observed for 5 to 70 days, during which period 2 ceased to pass viable ova, *i.e.*, they may have been cured.

The third group consisted of 4 patients infected with *S. mansoni*. They were given 0·4 gm. per patient on 4 alternate days and were observed for 50 days after which time only 1 patient was still passing viable ova. They were then given a second course consisting of 0·4 gm. on 5 successive days, after which the excretion of viable ova ceased.

The fourth group consisted of 6 children infected with *S. haematobium*. They were given 0·1–0·3 gm. every twelve hours for 5–6 days. Five weeks later the urines still contained living eggs and a second course with doses of 0·2–0·3 gm. was given. Living ova continued to be passed, although the proportion of degenerate ones increased.

A fifth group of 6 cases was treated with miscellaneous doses, and in most of them a temporary cessation of the excretion of eggs occurred.

A sixth group consisted of 14 patients who received 5 mgm. per kgm. every 12 hours if the urea clearance was above 50, and 2·5 mgm. per kgm. if it was below. Treatment was continued for 5–7 days. A fortnight later, all were still passing living ova.

It is concluded that miracil D is effective against both *S. haematobium* and *S. mansoni*, provided that a sufficient total dosage is administered during a

sufficiently short period, but although marked improvement is apparent, complete cure is not usually attained [by the dose schedules described in the present paper].

[The patients described in this paper seem to form an earlier series than those reported by HALAWANI, *et al.*, this *Bulletin*, 1948, v. 45, 797) in which doses up to 7·5 gm. during 8 days were employed; these doses cured 2 out of 3 patients. BLAIR, HAWKING, MEESER and ROSS (in press) have found in Southern Rhodesia that when children infected with *S. haematobium* were given 10 mgm. per kgm. daily for 10 days, 12 out of 18 were cured (15 weeks observation); some adults tolerated doses up to 1·6 gm. per person daily.] *F. Hawking*

ATKINS, W. R. G. **A Suggested Repellent for Schistosome Cercariae.** *J. Hygiene.* 1947, Dec., v. 45, No. 4, 468.

In this brief note the author suggests that copper soaps—particularly the greasy copper oleate alone or mixed with the firmer copper stearate or palmitate—may be effective repellents for schistosome cercariae. He has not tried them but suggests that experiments could be made at those bathing beaches in America where schistosome dermatitis is common. Copper is apparently more poisonous than mercury to certain worms (not pathogenic for man). If the soaps prove to be effective, they could be used by engineers, fishermen, and others working in water. Unguentum cupri oleatis B.P.C. is 12½ per cent. copper oleate in soft paraffin; it is unlikely either to irritate the skin or to be absorbed through the skin in toxic quantity. *Charles Wilcocks*

FIRLOTTE, W. R. **A Survey of the Parasites of the Brown Norway Rat.** *Canadian J. Comp. Med.* 1948, July, v. 12, No. 7, 187–91. [22 refs.]

The author, in the Institute of Parasitology, McGill University, Macdonald College, Quebec, examined 150 specimens of *Rattus norvegicus* for parasites.

The results are given in detail, and show that many species of parasites were found: the only ones of interest in human medicine, however, were *Hymenolepis diminuta*, *Capillaria hepatica* and, possibly, *Hymenolepis murina*, which were found respectively in 4, 6, and 16·5 per cent. *Capillaria hepatica* was diagnosed entirely by the finding of the characteristic eggs in the contents of the large intestine. *H. J. O'D. Burke-Gaffney*

COITO, A. de M. Contribuição para o estudo da epidemiologia do quisto hidático humano em Portugal. Sobre o grau de infestação dos cães errantes de Lisboa pela *Echinococcus granulosus*. [**The Epidemiology of Hydatid Cysts in Man in Portugal: Infection Rate of Stray Dogs in Lisbon with** *Echinococcus granulosus*.] *An. Inst. Med. Trop.* Lisbon. 1947, Dec., v. 4, 285–95. [19 refs.]

The English summary appended to the paper is as follows:—

"Studying the epidemiology of the human Hydatid Cyst in Portugal the author determined the rate of infestation by *Echinococcus granulosus* of the street dogs at Lisbon.

"At first he refers to the number of hydatid cyst cases registered in the two largest hospitals of Lisbon, during the period 1934–1943, the mean number of cases being 35·5 (0·11 per cent. of the patients) for the Civil Hospitals and 5·2 (0·16 per cent. of the patients) for the Hospital of the Medical School.

"In addition the author points out that in the 150 dogs observed he found 5 infested by *Echinococcus granulosus* (3·3 per cent.) and only 12 of those animals were not infected by helminths."

OEY OEN BIE. Een geval van Ileus door Ascariden veroorzaakt. [**A Case of Intestinal Obstruction caused by** *Ascaris*.] *Med. Maandblad.* Batavia. 1948, July 1, No. 24, 488–9.

The English summary appended to the paper is as follows :—

" Description of a case of intestinal obstruction due to Ascaris lumbricoides in a 3 years old Indonesian girl.

" The mass of worms which was located in the last 30 cm. of the ileum, near the ileo-colical valvula, consisted of 66 Ascaris lumbricoides (27 male, 39 female) and was removed by operation. Diagnosis as to the cause of obstruction could not be made before operation."

ERHARDT, A. Ueberblick ueber die medikamentöse Therapie der Askaridose. [**A Review of the Therapeutics of** *Ascaris* **Infections.**] *Med. Klin.* 1948, Feb., v. 43, No. 4, 114–17. [20 refs.]

WARTMAN, W. B. **Filariasis in American Armed Forces in World War II.** *Medicine.* 1947, Dec., v. 26, No. 4, 333–94, 33 figs. [55 refs.]

Pathological material, all from biopsies, was collected from every available source for the U.S. Army Institute of Pathology ; this forms the basis of the report. The clinical picture is drawn from numerous published reports and refers only to soldiers, sailors and marines in the U.S. services.

The patients were nearly all young men between the ages of 18 and 26. Most were infected in the Samoan Islands, the number from Wallis Island being unusually high. A few were infected elsewhere (*e.g.*, in the Solomon Islands). The average time spent in an endemic area was 11 months and the shortest time was one month. The usual incubation period was from 5 to 18 months, but adult worms were recovered in biopsy material within 3 months of the first exposure.

The onset was usually manifested by painful swelling of the scrotal contents, arms and legs, either singly or in combination. " Frequently the affected parts were swollen, red, and itched, and at times wheals were noticed. Although headache, backache, fatigue, and nausea were common, other constitutional symptoms such as fever, chills and malaise were unusual. Subjective symptoms were prone to develop suddenly, were mild to moderate in severity, often fleeting, and were characterized by remissions and exacerbations. Often patients had no symptoms at all and the disease was accidentally discovered during the course of a routine physical examination. In evaluating these symptoms it should be remembered that they were tabulated from statements made by the patients themselves, many of whom were suffering from battle fatigue or had considerable anxiety or even fear about the outcome of their disease ; the statements were no doubt influenced by these factors."

The most frequently encountered physical signs were lesions of the genitalia ; of these the commonest were funiculitis, epididymitis, orchitis, and scrotal oedema and inflammation. Hydrocele and varicocele were also relatively common, but chylous hydrocele and elephantiasis were not reported.

Lymphadenitis was the next most constant sign : the commonest groups were the inguinal, femoral, axillary and epitrochlear. In a few instances the cervical glands were involved, and rarely the subclavicular, popliteal and pectoral. A few observers reported generalized lymphadenitis.

Retrograde lymphangitis was common, but far less common than lymphadenitis with which it was usually associated : occasionally it was noted as occurring alone. The same areas were mainly involved. " There was very little febrile reaction ", and the associated pain was minimal.

Other physical signs included transient swelling and localized lymphoedema, urticaria, conjunctivitis, and mental manifestations, mainly anxiety states.

"Filarial fever" was not reported in early cases. In a few instances abscesses were reported; these were presumed to be filarial in origin. There was no evidence of sexual dysfunction.

"Attacks" were nearly always short, 3 to 5 days in duration; in many instances the signs and symptoms had disappeared in a matter of hours, and very rarely they lasted for longer than 2 weeks [except presumably the mental symptoms]. Relapses were relatively common; they were precipitated by "hard exercises, fatigue, and hot climate"; they occurred up to two years after infection. Lymphatic lesions in the experience of most writers persisted for some time after the return of the men to the United States, but having eventually subsided were seldom found after 20 months to 3 years, according to different observers, from the time the subject left the endemic area.

There are reports of the finding of microfilariae in the blood in 20 cases only: this includes one instance in which positive findings in 8 cases were reported, whereas 13 authors report no positive findings. In a total of 364 biopsies, adult worms or microfilariae were found in 78 (22 per cent.). The adults were all identified as *W. bancrofti*. Bacterial cultures of biopsies were almost without exception negative.

The white cell count averaged 9,000 per cmm. and eosinophilia occurred in one-half to two-thirds of the cases, averaging 850 per cmm. The blood sedimentation rate was usually unchanged.

Positive intradermal tests varied from 35 per cent. to 91 per cent. but most writers reported percentages above 80: *Dirofiliaria immitis* was used for preparing the antigen in most instances. False positives were uncommon, usually of the order of 5 per cent.; the test was only considered positive if both immediate and delayed reactions were noted. The reaction appeared early, usually prior to the first symptoms. Antigens made from other filarial worms, *e.g.*, *Setaria equina*, *Litomosoides carinii*, and the microfilaria of *W. bancrofti*, were also used with very similar results. Tests with antigens prepared from other nematodes, *e.g.*, *Ascaris*, gave less satisfactory results.

There is a detailed description of the pathological findings in biopsies from various sites including the epididymis, spermatic cord, testis, lymph nodes from various places, with and without worms, and lymph vessels. These are also presented in tabular form and are illustrated by beautiful photomicrographs. In ten lymph nodes adult worms were found, in 23 characteristic histological changes were found in the absence of worms, and in 24 others neither worms nor characteristic lesions were found. The following summary of the histological findings is quoted:—

"It is interesting to make a comparison of the tissue reactions associated with adult worms, and with microfilariae. In the former there is precipitation of strongly acidophilic material about the worms with necrosis of tissues, exudation of eosinophils, plasma cells and lymphocytes, and proliferation of macrophages and reticular fibers. In the latter there is no necrosis and the precipitate around the microfilariae, when it occurs, is amphoteric. Edema is conspicuous and the exudate is comprised chiefly of eosinophils. Macrophages and giant cells, although present, are not numerous and there is only slight reticular hyperplasia."

With reference to pathogenesis, two relevant quotations from the "Discussion" are given below:—

"As a result of the war experience clear evidence has accumulated that early filariasis is due solely to *W. bancrofti* and is not caused by bacteria or conditioned by their presence. Even after many months bacteria have not entered into the picture. Much other evidence indicates that *W. bancrofti* is

the etiologic agent, such as the demonstration of adult and larval parasites accompanied by significant lesions in involved tissues, the results of intradermal testing, and the clinical manifestations of the diseases."

"Many clinical manifestations of early filariasis such as blotchy redness of the skin, absence of severe constitutional symptoms, blood eosinophilia, and rapid appearance and disappearance of symptoms, are suggestive of hypersensitivity. During attacks of acute lymphangitis in one extremity there is not infrequently enlargement of lymph nodes in distant parts of the body such as the neck, groin or opposite extremity. The high incidence of positive skin tests, desensitization, passive transfer experiments, and reproduction of some of the characteristic signs and symptoms by intradermal injection of a suitable antigen, can all be explained on this basis."

[The paper as a whole constitutes a most important document on the early manifestation of filariasis and should be studied in the original.]

L. E. Napier

CHEN, K. C. **A Note on the Filaria Survey in Fukien Province.** *Lingnan Sci. J.* 1948, v. 22, Nos. 1/4, 85–92, 1 map. [12 refs.]

A questionary on the incidence of elephantiasis in Fukien province was sent out. The disease was reported in 38 *hsiens*, in 15 of which it was "especially prevalent". From 25 *hsiens* it was reported as absent.

Microfilarial surveys were carried out on a number of places in the province: blood specimens were taken between 9 p.m. and 11 p.m. The findings in the different locations are discussed in detail. In Foochow, hospital patients in whom the infection was suspected were examined and 40·1 per cent. of 207 patients were found infected. Many of these came from outside Foochow. In about one-third of the cases *Mf. malayi* was found. In other places, unselected prisoners, students or members of volunteer corps were examined. The microfilarial incidence varied from 30·0 per cent. (Changpu) to nil (Yungan and Shahsien). Incidences above 10 per cent. were found in Futsing (29·1 and 19·4 per cent.), Putien (14·5 per cent.), and Haiteng (12 per cent.)

The correlation between microfilaraemia and elephantiasis is not discussed, but the two *hsiens* showing no microfilaria do not appear in the list of those reporting elephantiasis, and of the three *hsiens* showing the highest microfilarial incidence two appear in the list of those with "especially prevalent" elephantiasis.

Mf. malayi was diagnosed in about one-fifth of the positive cases in the non-hospital groups; this infection is apparently widespread in the province.

A map shows the distribution of filarial infection as occurring along the coast-line and in the riverine areas.

L. E. Napier

HU, S. M. K. **Notes on the Experimental Infection of** *Culex pipiens* **var.** *pallens* **Coq. with** *Microfilaria malayi* **Brug.** *Lingnan Sci. J.* 1948, v. 22, Nos. 1/4, 79–83.

In Shanghai, between September 13th and 24th, 1940, *Culex pipiens* var. *pallens* were fed in three batches on a patient heavily infected with *Wuchereria malayi*. The average blood microfilaria counts during the times of feeding varied between 323 and 521 microfilariae per cmm. of blood.

In a total of 242 mosquitoes dissected between the 6th and 30th days after the infective feed, filarial larvae developed to the infective stage in only 5 (2·06 per cent.), and in each case there were only very few larvae. In 20 other mosquitoes, immature larvae were found; all of these except one were dead or completely encapsulated, and the remaining one had reached the second stage.

This observation confirms previous experiments and indicates that *Culex pipiens* var. *pallens* is a poor intermediate host of *W. malayi*. *L. E. Napier*

TOWNE, C. E. **Surgery of Elephantiasis of the Scrotum of Filarial Origin.** *New England J. of Med.* 1948, Aug. 5, v. 239, No. 6, 223–6, 1 fig.

BROSIUS, O. T., THOMAS, Esther E. & BROSIUS, Barbara. *Capillaria hepatica.* **A Case Report.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1948, July, v. 42, No. 1, 95–7.

Record of the case of a woman in Panama, 28 years of age, suffering for 4 days from very acute epigastric pain at short intervals accompanied by nausea and once by vomiting. In the stool were ankylostome and *Capillaria hepatica* ova. The family lived largely on "wild meat", including *conejo pintada*, a small amphibian rodent, and venison and birds; she was very partial to liver of the former. She denied eating peccary (an animal infested in nature by *Capillaria hepatica*) or monkey (the red spider monkey, *Ateles geoffroyi*, and the white-faced monkey, *Cebus capucinus imitator*, are both hosts of the *Capillaria*). The pain was relieved by morphine, oil of chenopodium was given for the hookworm; subsequent stool examinations failed to reveal any ova of *Capillaria hepatica*. *H. Harold Scott*

ERHARDT, A. E. Kritischer Beitrag zur Behandlung der Oxyuriasis. [**Critical Review of the Treatment of Enterobiasis.**] *Med. Klin.* 1947, Dec., v. 42, Nos. 23/24, 859–61. [23 refs.]

The author refers in this brief article to more than a score of vaunted remedies for *Enterobius* infestation. In assessing their value, one must be careful to distinguish relapse which may occur up to 8 weeks after the remedy is used (and implies failure to eradicate) and reinfection, indicated by appearance of ova in the stools later than this. He speaks most highly of Lubisan, resorcin-mono-butyl-ether-diethyl carbamate, which, according to report, succeeds in about 75 per cent. of cases. For many drugs of repute—helminal, butolan, santonin, ascaridol, gentian violet, among others—he has not a good word to say. He concludes that up to the present there is no absolutely reliable remedy; that all we can do is to treat symptoms, apply measures to prevent infestation or re-infestation, and that in time the infestation will clear up of itself. [Not very helpful, but probably quite true. A useful survey.]

H. Harold Scott

PIAGGIO BLANCO, R. A., FERNÁNDEZ CHAPELA, A. & PASEYRO, P. Triquinosis. [**Trichinosis.**] *An. Facul. de Med. Montevideo.* 1948, v. 33, Nos. 1/2, 135–60. [67 refs.]

A general review and account of a case.

DEFICIENCY DISEASES

DRILL, V. A. & LOOMIS, T. A. **Production of Functional and Fatty Changes in the Liver by a Chronic Vitamin B Complex Deficiency. and Interrelationships with Protein Intake.** *J. Nutrition.* 1948, Mar. 10, v. 35, No. 3, 333–48, 6 text figs. & 8 figs. on 1 pl. [21 refs.]

Liver damage has been produced in animals both by diets deficient in protein and by diets deficient in vitamins of the B complex. Often, however, the experimental conditions have not made it possible to distinguish between the effects

of these two deficiencies. One reason for this is that the appetite is often impaired, and with reduced food consumption there is inadequate intake of all nutrients. The experiments reported here were designed to overcome these difficulties. A chronic deficiency of the whole vitamin B complex was produced in dogs; the food intake was measured, and a control group was pair-fed, but given an adequate vitamin supplement. In this way the effect of inanition *per se* could be determined. To test the possibility of an interaction between protein and B vitamins in their effects upon the liver, the experiments were carried out at two levels of protein intake—normal (20 per cent. casein), and high (41 per cent. casein). Liver function was studied by serial measurements of bromsulphthalein retention and of serum phosphatase. These tests were chosen because they are in common clinical use. A single biopsy of the liver was made in each animal after about 30 weeks.

On the high protein diet, the vitamin-deficient animals had reduced appetite and lost weight. No histological or functional changes were found in the liver. In one dog there was proliferation of the capsular epithelium and crescent formation in the renal glomeruli. On the 20 per cent. casein diet, vitamin deficiency produced an increase in bromsulphthalein retention and serum phosphatase concentration. Biopsies of the liver taken at the 32nd week showed a moderate degree of fatty infiltration.

[The photomicrographs of these biopsies show a striking resemblance to that published by SEBRELL in his description of the "yellow liver" of ariboflavinosis in the dog. (SEBRELL, 1933, *Nat. Inst. Health Bull., No. 162*, p. 23).]

After the biopsies the dogs were given an adequate vitamin supplement, but kept on a restricted food intake. When they were killed 10 weeks later the livers were normal. In the inanition controls there were neither functional nor histological changes in the liver.

[These experiments have an obvious bearing on problems of human disease that have been discussed in recent numbers of this *Bulletin*. But it must always be remembered that, in the field of nutrition, the results obtained on one animal cannot be applied without reserve to another. It would be dangerous to conclude that in man avitaminosis can cause liver damage in the presence of a normal supply of protein. The authors do not imply this, but the discussion they give of their results is confusing.

Although in the dog both protein- and vitamin-deficiency may cause liver damage, the former seems to be the more powerful factor. In dogs given a very low protein diet with adequate vitamins, liver damage was much more severe and rapid in onset than that described above. (LI & FREEMAN, *Amer. J. Physiol.*, 1946, v. 145, 646).]

J. C. Waterlow

FERRO-LUZZI, G. Studio sui fenomeni di malnutrizione in Eritrea. Nota IIIa. Ricerche sperimentali su diete a base di dura (Andropogon sorghum), di taff (Eragrostis abyssinica) e di orzo. [**Nutrition Studies in Eritrea. III. Experimental Research with** *Andropogon sorghum, Eragrostis abyssinica* **and Barley.**] *Boll. Soc. Ital. di Med. e Igiene Trop.* (Sez. Eritrea). 1948, v. 8, Nos. 1/2, 54–61.

The numbers of animals subjected to experiment—white rats of 200–300 gm. weight—were few from which to draw valid deductions. Five (1 male, 4 females) were fed on taff (*Andropogon sorghum*) only; nine (5 males, 4 females) on dura (*Eragrostis abyssinica*) only, and 4 males on barley only; 18 animals altogether. Five lived for 12 months, nine for 9 months, one for 6 months, and two for 3 months only; one escaped after 6 months. Eleven were killed in the course of the investigations, 6 died of disease. All showed loss of weight and interference with fertility.

The author came to the conclusion that the effects were not the result of avitaminosis but of protein deficiency, especially amino-acids ; in other words, the proteins in these pulses are of " poor biological value " and unable to maintain a satisfactory nitrogen balance. Control animals receiving fresh vegetables in addition showed no signs of malnutrition. *H. Harold Scott*

ALTMANN, A. **The Syndrome of Malignant Malnutrition: (Kwashiorkor: Infantile Pellagra). Its Conception as a Protein Deficiency and its Treatment with Skimmed Lactic Acid Milk.** *Clin. Proc.* Cape Town. 1948, Jan., v. 7, No. 1, 32–53. [84 refs.]

Thirty cases are described of kwashiorkor in Bantu babies and children varying in age from three months to six years. They presented the characteristic clinical picture—loss of weight, dermatosis, lesions of mucocutaneous junctions, depigmentation of the hair, oedema, hypoproteinaemia, and normocytic anaemia of moderate severity. Although all cases had the typical rash, the author believes that this and other signs of vitamin deficiency are not essential features of the disease ; they are not always present, and bear no relation to the severity of the individual case. He contends that the main cause of the syndrome, which is in no way peculiar to the Bantu, is lack of protein and lack of calories, and that it closely resembles the condition known to paediatricians in Germany as *mehlnährschaden*, or " flour-feeding injury ".

In kwashiorkor, as in *mehlnährschaden*, there is a history of feeding on a mainly carbohydrate diet. In both there is oedema and fatty liver. The classical descriptions of *mehlnährschaden* mention muscular rigidity, which is a not uncommon feature of kwashiorkor. In some cases there is a reddish-brown pigmentation of the skin, which may be analogous to the kwashiorkor dermatosis.

If kwashiorkor, like *mehlnährschaden*, is a result of protein deficiency, it should be cured by a high protein diet. Dr. Altmann points out that " when using a therapeutic formula in nutritional disorders of babies, it is not only important to choose the correct formula, but also to apply it correctly ". The food he suggests is lactic acid skimmed milk. This was given in small quantities at first, increasing daily until 30–35 oz. were taken in 24 hours. On this treatment it was found that the frankly oedematous patients did well ; there were 22 cases of this type, and all recovered. The prognosis was much worse in those who were dehydrated or atrophic [the terms seem to be used synonymously]. Of 8 such cases, 5 died. No details of post-mortem findings are given.

The paper ends with a long and fully documented discussion, devoted mainly to oedema, the significance of fatty liver, and the results of treatment. Oedema is not an essential part of the syndrome, since the most serious cases are those in which it is absent or minimal. Nor is fatty liver pathognomonic of kwashiorkor, since it is found in infants dying of many other conditions. Even when fatty infiltration is present, there is no evidence that it causes serious functional impairment, or that death occurs from liver failure.

[Recent work on kwashiorkor is in agreement with Dr. Altmann's main conclusions—that the condition is a result of protein deficiency, that the signs of avitaminosis are inessential complications, and that there is a good response to treatment with milk alone. The comparison with *mehlnährschaden* has been made by others, but not so fully. It is of value, because it lifts kwashiorkor out of the realm of purely tropical diseases, and brings it into relation with the existing body of knowledge about the nutritional disorders of infants in temperate countries. This knowledge is far from complete, and will in turn be amplified by the work on kwashiorkor. If this position is accepted, it is only

logical to apply to kwashiorkor the classical principles of feeding evolved by paediatricians for the treatment of infantile malnutrition. Dr. Altmann is the first to do this explicitly.

Some of his conclusions on other points are, perhaps, open to criticism. He distinguishes between oedematous and dehydrated cases; reference to his tables shows that in all the dehydrated cases oedema was said to be present, comparable in severity and extent to that found in the waterlogged patients. There was also an equal reduction in the serum proteins: in 4 out of 6 dehydrated cases, the total protein was less than 4·0 gm. per cent. It therefore seems reasonable to look upon this dehydration not as a difference in kind, but as a complication, which, as in other diseases of infancy, is of grave omen.

The contention that liver function is not affected by the presence of fat cannot be accepted without reserve. Experimentally, functional impairment has been found in rats (MACLEAN *et al.*, *Brit. J. Exper. Path.*, 1937, v. 18, 345) and in dogs [above] with fatty livers. It has also been reported in human infants since Dr. Altmann's paper was published [WATERLOW, this *Bulletin*, 1948, v. 45, 724]. There are several observations in the literature of sudden death in coma in kwashiorkor, which are suggestive of death from liver failure [see HUGHES, *ibid.*, 1946, v. 43, 766]. *J. C. Waterlow*

ALLEMAN, R. J. & STOLLERMAN, G. H. **The Course of Beriberi Heart Disease in American Prisoners-of-War in Japan.** *Ann. Intern. Med.* 1948, May, v. 28, No. 5, 949–62, 3 figs. [26 refs.]

FLACHS, A. Nicotinamidterapi ved pellagrøs diarrhoe (" pellagra sine pellagra "). [**Nicotinamide Treatment of Pellagrous Diarrhoea, " Pellagra sine Pellagra."**] *Nordisk Med.* 1948, Aug. 13, v. 39, No. 33, 1507–9. [25 refs.]

The English summary appended to the paper is as follows :—

" 22 cases of diarrhoea observed in the medical department of the Old People's Home at Copenhagen were treated with niacin amide. All the cases had been treated previously with the ordinary obstipants without effect. None of the patients except 2 had had cutaneous pellagrous manifestations. In 17 cases the niacin amide therapy proved successful. In one of the cases that did not respond to the specific therapy, autopsy revealed a cancer of the colon. A dose of 15–30 mg. niacin amide per day was given and effects could be observed after 1–5 days. A case of ariboflavinosis is described in which treatment with lactoflavin led to an outbreak of pellagrous diarrhoea and the author points out the antagonistic action of the vitamins of the B group."

SPRUE

INNES, Elizabeth M. **The Blood and Bone Marrow in the Sprue Syndrome. A Study of 63 Cases.** *Edinburgh Med. J.* 1948, May, v. 55, No. 5, 282–92. [19 refs.]

From a review of the literature it is evident that the frequent occurrence of megaloblastic anaemia among cases of tropical sprue has been established. On the other hand, the blood picture in the sprue syndrome as met with in Britain is much less well-defined.

Sixty-three cases of the sprue syndrome have been studied. Seventeen could be classified as tropical sprue, 27 as non-tropical sprue and 19 as coeliac disease. It appears clear that the adult sprue syndrome is typically associated with

macrocytosis of the erythrocytes which may be accompanied by anaemia, but sometimes not. This statement applies equally to tropical as well as non-tropical sprue. The difference between them is one of degree, as the tendency to anaemia and macrocytosis is greater in the non-tropical group, but the bone marrow picture is characteristically megaloblastic when there is a marked degree of macrocytic anaemia. Occasionally this megaloblastic reaction may prove completely refractory to parenteral liver therapy, though usually this will improve the blood level and change the marrow picture either to the normoblastic or intermediate state. It would appear that the administration of liver results in a partial maturation of the megaloblasts. The process is, however, not complete and stops short of a complete transformation to the normoblastic state. The erythrocytes which result are reduced in numbers and are larger than normal, a fact which explains the persistent macrocytosis so characteristic of this condition. It is therefore suggested that some other factor is necessary for the complete restoration of normal erythropoiesis ; the nature and identity of this factor is unknown. In some cases, the factor might be folic acid, but in others the macrocytic anaemia persists despite its prolonged administration.

Macrocytic megaloblastic anaemias are extremely uncommon in childhood, so that it is not surprising to find among children with coeliac disease that the anaemia is characteristically of the hypochromic microcytic variety. In this case the marrow is normoblastic and appears capable of producing adequate numbers of erythrocytes, the defect being in their haemoglobinization ; but the cases failed to respond to the therapeutic administration of iron—a phenomenon which could be explained either by failure of absorption of iron from the bowel or by failure on the part of the marrow to utilize it.

In this series, one patient with coeliac disease responded excellently to intravenous injection of "Ferrivenin" (a proprietary preparation of saccharated oxide of iron). Therefore it is suggested that parenteral iron therapy may prove of great value in the cure of the iron-deficient anaemia of coeliac disease which persists despite prolonged oral administration long after the signs and symptoms of the syndrome have disappeared.

The two most urgent problems for solution are (1) the nature of the factor required for complete restoration of normal erythropoiesis in cases of sprue partially refractory to liver extract and folic acid, and (2) the mechanism underlying the failure of hypochromic anaemia of coeliac disease to respond to iron. *P. Manson-Bahr*

DICK, Margaret I. B., HARRISON, Isobel T. & FARRER, K. T. H. **The Thermal Stability of Folic (Pteroylglutamic) Acid.** *Australian J. Exper. Biol. & Med. Sci.* 1948, May, v. 26, Pt. 3, 239–44, 4 figs.

DICK, Margaret I. B., HARRISON, Isobel T. & FARRER, K. T. H. **The Microbiological Assay of Folic Acid.** *Australian J. Exper. Biol. & Med. Sci.* 1948, May, v. 26, Pt. 3, 231–7, 3 figs. [17 refs.]

VENOMS AND ANTIVENENES

BOQUET, P. Venins de serpents et antivenins. [**Snake Venoms and Antivenenes.**] Préface du Professeur Jules BORDET. Collection de l'Institut Pasteur. 157 pp., 12 text figs. & 4 figs. on 2 pls. 1948. Paris. Editions Médicales Flammarion. [400 fr.]

In this interesting memoir the author summarizes the results of researches on snake venom carried out in France and other countries during recent years.

After a brief historical account of the effects of snake bite, the venoms of viperines and colubrids are dealt with generally (opisthoglyphs excepted). The mechanisms of biting and the secretion of venom are briefly discussed and there is a very clear account of the present knowledge concerning the chemical structure and enzyme content of venoms and of their action on tissue enzymes. The action of physical and chemical agents on venoms is also described, and there are chapters on natural and acquired immunity, the treatment of snake bite and the therapeutic uses of venom. There is a short bibliography.

One chapter is of special interest. Therein the author has attempted to classify venoms according to their physiological and pathological properties. After tabulating variants of these properties such as coagulant, anticoagulant, haemolytic, etc., he groups venoms into four categories, namely: (1) Curarizing anticoagulants (type: *Naja tripudians*); (2) Curarizing coagulants (type: *Demansia textilis*); (3) Haemorrhagic anticoagulants (type: *Bitis arietans*); (4) Haemorrhagic coagulants (type: *Vipera russelli*). Group 1 contains the venoms of most of the colubrids of Africa and Asia and some of those of Australia; Group 2, the venoms of the Australian colubrids; Group 3, those of the viperines of Africa and America; Group 4 the venoms of the viperines of Europe, America, Asia and of the genera *Echis* and *Cerastes* of Africa.

The author points out the close similarity between the toxic actions of venoms and those of certain bacterial toxins with which the venoms appear to form "*familles naturelles*" in spite of their differing chemical and antigenic structures.

The book is extremely well arranged and clearly written and can be thoroughly recommended to all who are interested in snakes and snake venoms.

B. G. Maegraith

SARKAR, N. K. **Existence of a Cardiotoxic Principle in Cobra Venom.** *Ann. Biochem. & Exper. Med.* 1948, Jan.–Feb., v. 8, Nos. 1/2, 11–22, 12 figs. [18 refs.]

The author and others had previously observed that isolated toad heart was brought to a stop in systole by perfusion with crude cobra venom, but not by the various products isolated from the venom, such as the haemolysin. In the experiments described in this paper the author records the effects of perfusion of crude venom, haemolysin, neurotoxin and choline-esterase upon isolated toad and kitten hearts, and the action of crude venom on the circulation of cats (with and without artificial respiration). The author concludes that cobra venom has a definite toxic action on the heart, and that neurotoxin, choline esterase and haemolysin have not. The action of this cardiotoxic factor, which the author has labelled cardiotoxin 19, and claims to have isolated "in a pure and concentrated form", was further examined in isolated toad heart and intact anaesthetized cats. At a concentration equal to half the effective concentration of crude venom, the isolated heart was stopped in systole. Intravenous injection of a dose of "cardiotoxin" (equal to half the effective dose of crude venom) produced gradual fall of blood pressure to zero and slowing of respiration. Artificial respiration failed to revive the animal and the heart was eventually stopped in systole.

[In a general introduction to his paper the author states that in India 25,000 to 30,000 deaths occur every year from snake bite and claims that considerable numbers of deaths occur from the same cause in other countries including Africa and Australia. No authority is given for the latter statement, which is surely open to considerable doubt. It is difficult to accept the author's conclusions on the evidence submitted in the paper. For instance, although he states that haemolysin has no effect on the isolated heart, he records in Table IV

that a dose of non-crystalline haemolysin in a concentration of 1 in 50 caused a perfused toad's heart to stop in systole, whereas the same dose of crystalline haemolysin had no apparent effect. Table VI is headed "Amount of cobra venom required for the cardiac failure as indicated by the fall of B.P. to zero mm. (artificial respiration being used)". In a condition in which shock frequently predominates, measurement of cardiac failure in terms of fall of blood pressure cannot be reasonably accepted. However, at high concentrations of crude venom his published charts indicate some action on the heart, and the work should obviously be repeated more carefully in order to ascertain whether this effect is in fact due to a specific cardiotoxic principle.] *B. G. Maegraith*

TRETHEWIE, E. R. & DAY, A. J. **The Influence of Heparin on the Toxicity of Australian Snake Venom.** *Australian J. Exper. Biol. & Med. Sci.* 1948, Jan., v. 26, Pt. 1, 37–43, 2 figs.

Other workers have shown that heparin significantly reduces the toxicity of the venoms of the *Echis carinatus* and *Vipera russelli* [this *Bulletin*, 1947, v. 44, 846], both of which have coagulant effects. The authors report the results of an investigation of the effects of heparin on the thrombotic activity of the venoms of two Australian snakes, *Notechis scutatus* and *Pseudechis porphyriacus*. Tiger snake (*Notechis scutatus*) venom was injected subcutaneously into guinea-pigs in about double the LD_{50} dose and heparin was injected immediately afterwards and thereafter daily. Control series were injected with venom alone. Venom of *Pseudechis porphyriacus* was injected into mice by means of a similar technique. In both sets of animals the death time was measured. Heparin did not affect the toxicity of either venom, but prolonged the death time in heparinized animals. The authors point out that "in Australian snake venoms there appear to be three distinct principles, namely, formation of lysolecithin, a thrombotic and a neurotoxic principle". They suggest that these three elements may act at separate times, the thrombotic and lysolecithin effects acting first. Heparinization might inhibit the thrombotic effect and allow the more slowly acting neurotoxic principle to kill, so lengthening death time. Alternatively, the three elements of the venom might act together; the heparin, by minimizing one of them, might extend the period of life. After doses near the LD_{50}, heparin did not allow survival but merely prolonged life. The authors suggest that heparin might be useful therapeutically in that the life of persons suffering from black-snake or tiger-snake bite might be prolonged by its administration so that other forms of treatment of known value might be given more opportunity to act. *B. G. Maegraith*

VACHON, M. Etudes sur les scorpions. Chapitre III. Description des scorpions du Nord de l'Afrique (Maroc, Algérie, Tunisie, Sahara algérien et Fezzan). [**Studies on Scorpions. III. Descriptions of North African Scorpions.**] *Arch. Inst. Pasteur d'Algérie.* 1948, June, v. 26, No. 2, 162–208, figs. 87–147.

EARLE, K. V. **Injuries produced by Tropical "Water-Beetles".** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1948, July, v. 42, No. 1, 101–4, 2 figs. [10 refs.]

In Ecuador three species of water-beetles are found: *Lethocerus camposi*, up to 3½ inches in length; *L. annulipes*, to 2½ inches, and *Belostoma boops*, to 1 inch. They live on aquatic insects, fish and frogs, and may attack and kill birds. They are attracted by bright lights and in the rainy season may leave the ponds, sewers and marshes for the land and are found congregated at the base of lamp-posts. They do not as a rule bite man unless handled. The bite of the largest is painful and causes at first blanching, then swelling, redness

and throbbing ; these usually clear up in 24 hours, but occasionally cellulitis and abscess follow. Treatment is symptomatic : ammonia locally in the early stages ; later, if there is suppuration, sulphonamides or penicillin. The existence of poison glands is uncertain ; there are two pairs of glands lying lengthwise along the oesophagus and, just above the beak, the cephalic glands, the homologues of the maxillary glands. Whether any of these produces venom has yet to be determined. The ventral and dorsal aspects of the largest water-beetle, the first-named, are well reproduced in two photographs.

H. Harold Scott

DERMATOLOGY AND FUNGUS DISEASES

AGUIRRE PEQUEÑO, E. & GONZALEZ, R. E. Mal del pinto. (Bibliografia.) [**Bibliography of Pinta.**] *Medicina.* Mexico. 1948, July 10, v. 28, No. 559, 257–315.

This immense compilation occupies more than 50 pages and is evidence of very great industry and patience. After a brief introduction, the authors give a lengthy list of synonyms for this disease, shown topographically for different American countries. The bibliography is then presented in alphabetical order of authors and this occupies 18 pages ; a chronological bibliography from the year 1525 to 1948 takes another 18 pages ; then follow bibliographies relating respectively to geographical distribution, aetiology, epidemiology, inoculation experiments, possible vectors, clinical features, pathology, differential diagnosis, serology and treatment. Further short bibliographical references deal with historical work, monographs, theses, general papers, books and commentaries ; the last named includes references to *Pinta* in this *Bulletin* from 1913 to 1946. The very large number of contributions to the literature by the senior author himself is additional evidence of his wide knowledge and experience of his subject.

This paper constitutes a very useful conspectus of the literature of pinta.

H. J. O'D. Burke-Gaffney

DELAMATER, E. D. **Technic and Identification of Fungi of Medical Interest.** *Amer. J. Clin. Path.* 1948, Mar., v. 18, No. 3, 235–46, 3 figs. [13 refs.] [Summary appears also in *Bulletin of Hygiene.*]

The pathogenic fungi which may occur in various human materials are tabulated and methods for direct observation and culture are briefly described. The indiscriminate use of the so-called Sabouraud's medium is criticized. Though this medium is suitable for primary isolation of the dermatophytes and of *Candida*, the use of cornmeal agar, dextrose nutrient agar, blood agar and thioglycollate broth for other fungi is described. Bacterial contaminants may be prevented by penicillin-streptomycin medium, but it is not possible to inhibit the growth of saprophytic fungi. The mouse is a valuable diagnostic animal for routine use and, while it may be essential in the isolation of *Sporotrichum* and of *Coccidioides*, it is useful also in confirming the diagnosis of infections by other fungi.

The paper concludes with a short description of each of the important disease-producing fungi and is illustrated by photographs. The author states that " actual culture and identification of the dermatophytes is not essential to either the diagnosis or the treatment of the ringworm diseases " and that the complicated methods used by Conant and others for the identification of *Candida albicans* are unnecessary. *Histoplasma capsulatum* may be closely

simulated by minute budding cells of *Candida albicans* in smears. The differentiation of *Actinomyces bovis* from *Nocardia asteroides* is clinically important in view of their different drug sensitivities. *R. W. Riddell*

BOURGAIN, M. & BAZIL, A. Onychomycose à favotrichophyton d'origine exotique. Coexistence de deux jordanons de type achorion. [**Tropical Favus of the Nails : Co-existence of Two Jordanons of** *Achorion*.] *Rev. Méd. Nav.* (*Métropole et Outre-Mer*). Paris. 1948, v. 3, No. 2, 185–8.

Brief clinical details are given of a case at Cherbourg of favus of the nails in a ship's electrician who had developed this rare condition abroad. The causal fungus was obtained in culture in two forms which were considered to correspond with *Achorion brumpti* and *A. milochevitchi* of LANGERON and BAEZA [see this *Bulletin*, 1937, v. 34, 178], two jordanons [near species] of *A.* [*Trichophyton*] *schoenleini*. *G. C. Ainsworth*

DE MEIRA, M. T. V., SIMÕES, T. S. & NOGUEIRA, J. F. P. Sobre a existência do " pé musgoso " na Ilha de S. Nicolau (Cabo Verde). [**The Presence of " Mossy Foot " in S. Nicolau, Cape Verde Islands.**] *An. Inst. Med. Trop.* Lisbon. 1947, Dec., v. 4, 269–79, 9 figs. on 4 pls.

The English summary appended to the paper is as follows :—

" The authors found 21 cases of ' mossy foot ' in the island of S. Nicolau (Cape Verde Islands).

" They refer to the history of the disease and to the symptoms of several groups of patients.

" Finally they present the first results of the bacteriological, histological and X-ray examinations performed in 3 patients."

NEGRONI, P. & RADICE, J. C. La formación de endosporos en el coccidioides immitis observado con la luz de Wood. Su posición sistemática. [**The Formation of Endospores in** *Coccidioides immitis* **observed with Wood's Light. The Systematic Position.**] *Rev. Argentina Dermatosifilologia.* 1947, July–Dec., v. 31, Nos. 3/4, 573–8, 3 figs. [21 refs.] French summary.

do SNYDER, B. L. & ROGERS, G. K. **Disseminated Coccidioidal Granuloma (Case Report).** *Arizona Med.* 1948, Mar., v. 5, No. 2, 33–7.

The disseminated form of infection by *Coccidioides immitis*, which carries a mortality rate of more than 50 per cent., constitutes only 0·2 per cent. of all cases of coccidioidomycosis. The primary, or pulmonary, form is prevalent in Arizona and is usually non-fatal.

The case history is described of the disseminated disease in a young adult white male who had resided in Arizona for 3 years. He complained of fatigue, cough, fevers, muscular aches and loss of weight, and examination revealed an upper lobe pulmonary lesion. Three months later cutaneous coccidioidomycosis had developed over the chest and face and grew progressively worse. The coccidioidin test and specific serological reactions were negative. Raised intracranial pressure led to death of the patient about one year after his initial hospital attendance. The cerebrospinal fluid had shown an increase in protein and lymphocytes, but culture was negative.

A wide distribution of coccidioidal granulomata was demonstrated at necropsy ; the liver was not obviously involved. Cerebrospinal lesions were limited to the meninges, where fungus spherules tended to be larger and more actively proliferating than elsewhere. The clinical and pathological features of the cutaneous disease are discussed. *R. W. Riddell*

TROPICAL ULCER

D'ALMEIDA, J. Sept cas de cancers greffés sur ulcères phagédéniques à l'Hôpital Central en 1946. [**Seven Cases of Cancer Superimposed on Tropical Ulcers in the Central Hospital in 1946.**] *Bull. Méd. de l'Afrique Occidentale Française.* 1947, v. 4, No. 2, 99–103.

HARE, K. **Studies in Tropical Ulcer. Part I. The Origin of an Epidemic.** *J. Trop. Med. & Hyg.* 1948, Mar., v. 51, No. 3, 47–53, 4 figs. [7 refs.] **Part II. The Aetiology of Tropical Ulcer.** *Ibid.* Apr., No. 4, 72–81. [18 refs.] **Part III. The Insect Vector.** *Ibid.* May, No. 5, 99–103. [12 refs.] **Part IV. The Treatment of Tropical Ulcer.** *Ibid.* June, No. 6, 119–28. [26 refs.]

I. In this paper the term " tropical ulcer " is reserved for acute ulcers having a phagedaenic tendency and which are characterized clinically by a foul smell and an adherent slough overlying a soft granulomatous base that bleeds easily. Bacteriologically, the fusiform bacillus is constantly found whatever other organisms may be present.

The Tingri district in Assam, in which the work reported was carried out, covers an area of about 144 square miles, and is almost absolutely flat, the soil being the usual alluvial silt of the Brahmaputra valley. In it are found 20 tea estates, areas of forest and scrub jungle, rice land, and scattered native villages. The population consists chiefly of aboriginals from Central India with some Nepalese and Assamese in the villages. November to February are dry and comparatively cold, March and April are warmer with scattered rainfall, and May to October hot and humid with a fairly high rainfall. The average yearly rainfall is about 95 in., of which about 85 in. fall during the latter period. Shade temperatures are not above 100°F. but humidity percentages of 90 and over are common.

Up to 1941 tropical ulcer was very rare in this district. About 1942, gangs of labourers were sent to the oilfields for jungle clearing and to various military works.

The author gives a table of the incidence of the disease in 1946 in 13 estates on which he worked. Out of a total estate population of 20,699, 1,101 cases (5·32 per cent.) were met with, but the condition was also widespread in the neighbouring villages. From a study of the incidence on tea estates it was noticed that an appreciable period elapsed between the appearance of the disease in one line and its spread to another. Study of the figures for 13 estates in each month of 1946 showed that during the 4 cold dry months (November to February) the incidence was nil. There was therefore no carry-over of cases from one season to the next and maintenance of the infection cannot be blamed on isolated sporadic cases during the cold months. All authorities appear to agree that natural or acquired immunity does not occur in tropical ulcer.

The paper is illustrated with five tables and four figures, and these include figures for the incidence of tropical ulcer from 1942 to 1946, inclusive.

II. The author considers that : (1) Tropical ulcer is a specific disease associated with infection by the fusiform bacillus. Under ordinary conditions only man is susceptible, experimental infection of the ordinary laboratory animals having been found impossible. One observer, however, states that the Nigerian hedgehog is susceptible (SMITH, *Trans. Roy. Soc. Trop. Med. & Hyg.*, 1936, v. 30, 259). There is no evidence that a filterable virus is responsible [this *Bulletin*, 1946, v. 43, 378].

(2) The condition is confined to warm countries and to seasons of moderate heat and rainfall. The disease disappears under conditions of extreme heat, cold, and excessive drought and rainfall.

(3) Tropical ulcer can be maintained in a population without any carry-over of cases from one season to the next. As the causal bacillus is difficult to culture and is easily destroyed, it is unlikely that infected fomites or dust carry the infection, and there is no evidence that it is harboured by animals. The human mouth is probably not an important agent in carrying the infection, and is certainly not an important factor in its dissemination.

(4) Infection is confined almost entirely to adults and older children, but the type of work being done is not of primary importance. The disease is one of rural or semi-rural living conditions, but needs a reasonable density of population for its spread.

(5) Although some degree of trauma probably always precedes the appearance of an ulcer, this may be very slight.

(6) In an area where tropical ulcers are prevalent, certain sub-areas are much more heavily infected than others.

(7) There is no definite evidence that tropical ulcer is a deficiency disease, and neither malaria nor alcoholism appears to play any important part in its causation.

(8) The majority of tropical ulcers appear on a limited area of the body, but it is very doubtful whether the explanation advanced that this area is one of deficient blood supply is correct.

(9) The seasonal character of the disease and its predilection for one particular class and for certain geographical areas suggest that the infection is carried and harboured by an insect vector. The limited portion of the body normally affected suggests that this vector is a crawling insect.

III. For many years in Assam it has been the opinion of medical men, especially those working on tea estates, that tropical ulcer is an insect-borne disease. This has been more a matter of conjecture than the result of a close study of epidemiology, the most widely held view being that abrasions are infected by various flies which have previously settled on existing ulcers and act merely as mechanical transmitters. The eye-fly (*Siphunculina funicola*) has been incriminated, mainly owing to its close seasonal incidence with the disease. In only one case did a medical man succeed in infecting himself by allowing one of these insects to feed on a typical ulcer and then transferring it to an abrasion on his own body. Subsequent observers were uniformly unsuccessful, and moreover the disease is frequent in districts where the fly is unknown.

The average estate labourer's house is full of such insects as the cockroach, bed bug, louse, flea, sandfly, and housefly. These are more likely to attack children than adults, but it is known that the former are rarely affected. Adults usually defaecate in some patch of scrub jungle not far from their houses, passing through moderately long grass on the way. Children under the age of 6 usually defaecate in the close vicinity of their houses on bare earth, and the older ones up to 12 on the roads adjacent to the coolie lines. There is thus a marked correlation between the sanitary habits of the various age groups and the incidence of the disease.

Outdoor winged insects bite any part of the body indiscriminately and, other things being equal, if these were incriminated it would be expected that tropical ulcer would appear anywhere on the body, but in fact over 95 per cent. of cases are confined to the leg, ankle, and dorsum of the foot.

The argument is put forward that the vector is a crawling insect which lives mostly in jungle or coarse vegetation and can retain an infection from one year to another. Ticks and mites are the insects which best fulfil these requirements, and are probably found in all countries where tropical ulcer is known. It has been established that they are capable of retaining certain infections from year to year. If the hypothesis is accepted that a tick or mite is the vector, the

almost universal finding of ulcers below the knee is capable of a simple mechanical explanation, namely, as a man walks through long grass or bush most of the insects attaching themselves to the foot are brushed off, but any above the ankle tend to remain there. Further, the leucocytic infiltration into the base of the ulcer consists largely of eosinophiles, and this has been found to be very characteristic of lesions caused by the bites of harvest mites and various species of ticks. Again ulcers are most frequent among the strongest labourers, these being the people who go most into the jungle to cut firewood and hunt game.

IV. The results of various methods of treatment and the literature on the subject are reviewed very fully.

The author decribess the treatment of 483 cases, all being of the typical acute type. In 184 instances more than one ulcer was present, the number varying from two to eleven, while in this series both legs were affected in about one-third of cases.

Eight different methods of treatment were tried and are described in detail. The criterion of cure was firm and complete healing in 47 days, and the following routine treatment was found to be most satisfactory. After preliminary cleansing with sterile normal saline, the ulcer is dressed twice daily for five days with sterile gauze moistened with a solution of 500 units of pencillin per ml. On the first day of treatment, 100,000 units of penicillin are given intramuscularly in five three-hourly injections. From the sixth day onward, the ulcer is dressed daily with scarlet-red ointment, but at the slightest sign of the sore becoming foul again the local penicillin dressing is repeated for three or four days. If serious reinfection has occurred it is advisable to repeat the parenteral administration of penicillin, but each case should be treated on its merits. No difference was apparent in giving more than 100,000 units in any one course and the value of this drug is particularly apparent in ulcers over 1 inch in diameter. In the case of the larger ulcers skin grafting helps to reduce the time required for epithelialization.

One difficulty of penicillin treatment is that some form of refrigerator is necessary unless very large numbers of patients are being dealt with, when the whole contents of one phial can be used immediately it has been dissolved, as otherwise there will be much wastage. In the absence of penicillin the smaller ulcers can best be treated with the copper sulphate, phenol and glycerin paste method, followed by a choice of cod liver oil, acriflavine emulsion or scarlet-red ointment [this *Bulletin*, 1938, v. 35, 828]. The author apparently does not use surgical débridement. Of 128 cases treated by penicillin, 79·7 per cent. were regarded as successes; with single ulcers of 1 inch or more in diameter, 84·2 were successful. [For descriptions of the comparative methods of treatment tested, the original paper should be consulted.] *C. F. Shelton.*

MISCELLANEOUS DISEASES

CHALGREN, W. S. & BAKER, A. B. **The Nervous System in Tropical Disease. A Clinical Review.** *Medicine.* 1947, Dec., v. 26, No. 4, 395–439. [402 refs.]

This paper is a review and not suitable for abstraction; it should be referred to in the original by those particularly interested in the diseases discussed, namely, yellow fever, dengue, epidemic and endemic typhus, Rocky Mountain spotted fever, tsutsugamushi disease, Q fever, bartonellosis, bacillary dysentery, cholera, plague, melioidosis, leprosy, malaria, African trypanosomiasis, South American trypanosomiasis, leishmaniasis, relapsing fever, rat-bite fever, amoebiasis, ascariasis, hookworm infection, filariasis, schistosomiasis, and paragonimiasis.

In each case a thumb-nail sketch is given of the disease as a whole and this is followed by a review of references to "neuropsychiatric manifestations and complications" that have appeared in the literature. The subject, however, is treated mainly from the point of view of the organic neurologist and, for example, the well-known neuropsychiatric manifestations associated with filariasis (Bancroft's) are not discussed.

Naturally, the sections vary in length: there are for example 54 references in the malaria section, most of which are of recent date, whereas the author has only been able to muster 4 for Bancroft's filariasis and they are all 20 or more years old; three of these refer to the finding of microfilaria in the blood vessels of the brain, and only one, an unimportant one, suggests that there are any associated symptoms.

The paper is a very laborious piece of work. *L. E. Napier*

PROTOZOOLOGY: GENERAL

WARREN, J. & RUSS, Sudie B. **Cultivation of Toxoplasma in Embryonated Egg. An Antigen derived from Chorioallantoic Membrane.** *Proc. Soc. Exper. Biol. & Med.* 1948, Jan., v. 67, No. 1, 85–9, 1 fig.

By means of toxoplasma-infected chorio-allantoic membranes from infected chicken eggs complement-fixing antigen was prepared. The membranes were ground in a mortar with alundum and a 10 per cent. suspension was prepared in physiological saline buffered at *p*H 7·4. The crude suspension was frozen and thawed three times and clarified by 15 minutes' centrifugation at 3,500 r.p.m. The supernatant fluid, after the addition of merthiolate to 1 : 10,000, constituted the antigen. This was generally stored at −20°C. An antigen for use as control material was prepared in the same way from normal 16-day-old chick embryos. Sera were obtained from rhesus monkeys and guineapigs convalescing from a toxoplasma infection and from a number of patients suspected of suffering from toxoplasma infection. The fixation tests were performed as follows:— In tubes were placed 0·25 cc. of the dilution of serum, 0·25 cc. of the antigen and 0·5 cc. of fresh diluted guineapig serum containing two units of complement. They were incubated at 5°C. overnight. The haemolytic system, consisting of 0·5 cc. of a mixture of equal parts of 3 per cent. suspension of washed sheep erythrocytes in saline and diluted amboceptor (2 units) was added to the tubes. They were incubated at 37°C. for half an hour and read in the usual manner. The immune animal sera were positive (1 in 200 to 400) as also were human sera from both proven and suspected cases of toxoplasmosis (1 in 16 to 128). *C. M. Wenyon*

MACFARLANE, J. O. & RUCHMAN, I. **Cultivation of Toxoplasma in the developing Chick Embryo.** *Proc. Soc. Exper. Biol. & Med.* 1948, Jan., v. 67, No. 1, 1–4, 2 figs.

Inoculation of toxoplasma—the "R.H." strain of SABIN—in the yolk sac of chicken eggs of 7 to 11 days' incubation resulted in the death of the chicken embryo on the 5th to the 6th day. Examination of the eggs showed numerous yellow-white plaques, 0·5–3 mm. in diameter, on the chorio-allantoic and amniotic membranes. The areas surrounding the lesions were thickened and histologically represented regions of dense cellular infiltration containing numerous toxoplasma. Smears of the membranes revealed numerous toxoplasma, which were also present in the organs of the embryo. Inoculation of the parasites into mice, rats, chicks, rabbits and rhesus monkeys

produced infections which did not vary from those produced by inoculation of the original strain from the mouse. The passage through the chick embryo did not modify the parasite in any way. Attempts to cultivate the toxoplasma in the pooled embryonic fluid from 17-day fertile eggs were unsuccessful. Storage of infected membranes at 4°C. yielded viable organisms up to one month. Photographs illustrate the appearance of the normal and infected chorio-allantoic membrane and the difference between microscopic sections of these. *C. M. Wenyon*

WINSSER, J., VERLINDE, J. D., VAN THIEL, P. H., DAVEL, J. & VAN DER ELST, P. **Isolation of Toxoplasma from Cerebrospinal Fluid of a Living Infant in Holland.** *Proc. Soc. Exper. Biol. & Med.* 1948, Mar., v. 67, No. 3, 292–4.

The diagnosis of toxoplasmosis is frequently made on the evidence of serological reactions and the presence of ocular changes in the patient. Final confirmation by demonstration of the organisms is much less frequent and seldom achieved, as it was in the case under review, during life.

The patient, a child six weeks old on admission to hospital, appeared healthy during the first few weeks of life. When first seen in hospital he presented marked ocular changes, displacement and enlargement of the lateral ventricles and developing hydrocephalus.

The centrifuged deposit of the cerebrospinal fluid, when examined microscopically, showed numerous toxoplasma bodies. The cerebrospinal fluid, inoculated intracerebrally into mice, produced infections in the latter.

The serum of the child's mother showed strong neutralizing power against the organism when examined by Sabin's rabbit skin test. Cross immunity tests for neutralizing activity between the organism isolated and another human strain from America showed that the two strains were very closely related, if not identical. *H. E. Shortt*

ENTOMOLOGY AND INSECTICIDES: GENERAL

CALLOT, J. La réaction de l'homme aux piqures de moustiques. [**Man's Reaction to Mosquito Bites.**] *Ann. Parasit. Humaine et Comparée.* 1947, v. 22, Nos. 3/4, 233–4.

The author refers to the notes on this subject by MELLANBY [this *Bulletin*, 1947, v. 44, 240 and 364], by BRISTOWE and by RIBBANDS [*ibid.*, 364] and in general confirms their conclusions on relative attractiveness or otherwise of different persons to mosquitoes.

In his experience with *Aëdes aegypti*, however, a person who is re-bitten continuously by this mosquito after an interval of several months presents a delayed reaction (Mellanby's Stage I): after another interruption of 40 days, followed by a new series of bites, he passes directly into Stage III, and this state persists for three months despite daily bites.

On the other hand, experiments with *Culex autogenicus* Roubaud, showed that the reaction produced in this case after the initial bite was that of Stage II, without Stage I having been entered at all.

The author has never succeeded in obtaining Stage IV experimentally: he suggests that some people attain it, while others are free from any reaction from the outset. He draws a distinction between those who "have never been bitten by mosquitoes" and those who do not react to the bites, and gives an example of a subject who had never been in contact with *Aëdes aegypti* but suffered no reaction whatever when he was bitten experimentally by this species. *H. J. O'D. Burke-Gaffney*

ABBOTT, P. H. **The Culicidae (Diptera) of Darfur Province, Anglo-Egyptian Sudan, with Observations on the Geography and Zoogeographical Relations of the Region.** *Proc. Roy. Entom. Soc. London.* Ser. B. 1948, Apr. 26, v. 17, Pts. 3/4, 37–48, 1 map. [10 refs.]

Darfur is the most westerly province in the Sudan. It lies at the northern limit of the Ethiopian region and includes the Marra mountains rising to over 10,000 feet.

The topography and climate are described and notes are given on the distribution and breeding places of the mosquitoes. The majority of the mosquito records were made in the dry season [year not stated] as travel is almost impossible in the wet season. Nine species of *Anopheles* and twenty-seven culicines were collected. *A. gambiae* is the commonest anopheline and the only malaria vector in the area. Other mosquitoes whose presence in Darfur is of particular interest are *Anopheles rupicolus* and *Aëdes arabiensis*, not previously found so far west as this ; *Culex laticinctus*, known from Arabia, E. Africa and the Mediterranean region ; and *Culex grahami*, previously known only in the west, southern Congo and Uganda. *Aëdes aegypti* was widely distributed in the province. *H. S. Leeson*

DE MEILLON, B. **New Records and Species of Biting Insects from the Ethiopian Region. II.** Reprinted from *J. Entom. Soc. South Africa.* 1947, Aug. 30, v. 10, 110–24, 4 figs.

The new species described in this paper include a mosquito *Anopheles mascarensis* male and female from Madagascar ; two Ceratopogonidae, *Culicoides acastus* male and *Alluaudomyia transvaalensis* female, both from the Transvaal ; and the males and females of five fleas, from various parts of Southern Africa, *Xenopsylla pasiphae*, *X. mulleri*, *X. achilla*, *X. bechuanae* and *Chiastopsylla capensis*. A list is given of 12 Anopheline and 22 Culicine mosquitoes collected in Bechuanaland. *H. S. Leeson*

LICHTENSTEIN, E. P. **Growth of *Culex molestus* under Sterile Conditions.** [Correspondence.] *Nature.* 1948, Aug. 7, 227.

STAGE, H. H. **A Vespid preying on Anophelines.** *Mosquito News.* 1948, June, v. 8, No. 2, 73.

FAY, R. W., COLE, E. L. & SIMMONS, S. W. **Toxicity of DDT Residues. Effect of Surface and Surface Treatment on the Residual Toxicity of DDT against Adult *Anopheles quadrimaculatus* Mosquitoes.** *Soap.* New York. 1948, June, v. 24, No. 6, 130–33, 157–9, 189, 3 figs.

These experiments constitute an extension of earlier work and the same technique was employed [see CLAPP, FAY and SIMMONS, this *Bulletin*, 1947, v. 44, 563 ; SIMMONS *et al.*, *ibid.*, 1946, v. 43, 789 ; FAY, SIMMONS and CLAPP, *ibid.*, 1947, v. 44, 562]. In brief, adults of *Anopheles quadrimaculatus* were exposed for sixty minutes in a small box, the sides of which are made up of various materials (in different tests) and treated with DDT at the rate of 200 mgm. per sq. ft. The surfaces investigated were, plain pine plywood (standard), dry bamboo, rusty metal screen, rusty sheet metal, bark, new sheet metal, glass, tile, palmetto thatch, new metal screen, "plexiglass", shellacked wood, synthetic fabric, cement and waxed wood. DDT was sprayed on as a xylene-Triton X emulsion, as a kerosene solution or as an aqueous suspension.

The results indicated a better persistent toxicity (up to forty-five weeks) on relatively rough surfaces (rusty metals, bark) " which might be expected to aid

spray coverage and adherence ". Smooth but impermeable surfaces were next in order of efficiency, and least satisfactory were either waxed or shellacked surfaces (which might have softened and absorbed DDT) or else very porous materials (cement).

These results were true, generally speaking, of treatments with emulsion and kerosene solution. The suspension of the DDT-wettable powder was definitely better on the absorbent cement and somewhat better on the new metal and glass; it gave inferior results on the rough surfaces of rusty metal and bark.

Various household cleansing measures were tested for their effects in reducing residual toxicity of DDT films. With fabrics, dry cleaning was most drastic, followed by vigorous brushing and (least serious) vacuum cleaning. DDT was removed from walls by periodic dusting, and more rapidly if a paste cleaner was employed. *J. R. Busvine*

RAFFAELLI, D. Determinazione colorimetrica del DDT sull'intonaco delle pareti trattate. [**Colorimetric Estimation of DDT on Treated Walls.**] *Riv. di Parassit.* Rome. 1948, June, v. 9, No. 2, 79–83. English summary (2 lines).

The following method, derived from Chaikin's reaction (*Ind. Eng. Chem.*, Analytical Ed., 1946, v. 18, 272) is useful for rapid estimation of DDT present on walls and other surfaces sprayed for residual insecticidal effect.

The superficial layer of surface is scraped from 100 sq. cm. on to a piece of paper and thence transferred to a test tube. The DDT is extracted with about 4–5 ml. of ether which is decanted into another tube. This tube is placed on a water bath and the extract is evaporated to dryness. To the residue, 2 ml. of glacial ascetic acid are added and the tube is warmed for a short time on the bath with agitation; then 10 ml. of sulphuric acid (D 1·84) are added and the mixture is heated on the bath for ten minutes.

The presence of DDT is indicated by a yellowish colour with a tinge of green, the depth of colour indicating the amount of DDT present. For quantitative work, standards are made up with 0·25 to 5 milligrammes of DDT. The colours produced in this reaction are then matched by dilutions of a solution of Grübler meta chrome yellow 2 R.D. to which a trace of Grübler methyl green has been added. These solutions are kept as reference standards.

This method is accurate if the DDT application has been made with a kerosene solution. When an emulsion or dispersion has been employed, there may be traces of emulsifying or dispersing agents which introduce a brownish tinge, sufficient to interfere with a quantitative determination. This can be avoided as follows: The deposit from the ether extract is treated with a few ml. of concentrated potassium permanganate and placed on the water bath to evaporate to dryness. A new ether extraction is then made and the test is conducted in the usual way. *J. R. Busvine*

SCOTT, J. A. **An Apparatus for removing Tropical Rat Mites from Large Quantities of Bedding Materials.** *J. Parasitology.* 1948, Apr., v. 34, No. 2, 132–3, 1 fig.

This apparatus was constructed for the purpose of extracting within a single working day large numbers of adult and nymphal tropical rat mites (*Liponyssus bacoti*) from about 4,000 cc. of wood shavings and an equal volume of hay. It consists of an open trough of galvanized sheet iron (3 ft. 8 in. × 8 in. × 4 in. deep) surrounded by a moat containing water maintained at a depth of ¼ in. An infra-red bulb of 250 watts suspended over the trough moves along at the rate of ½ in. per hour. The mites are driven ahead of the wave of heat and are

collected by means of a suction bottle. The bottom of the trough is lined with asbestos cement to delay heat conduction and prevent mites being killed when they drop off the ends of pieces of hay. A line drawing illustrates the apparatus and gives all necessary dimensions ; it also shows a simple device for collecting mites which fall into the water in the moat. *H. S. Leeson*

REPORTS, SURVEYS AND MISCELLANEOUS PAPERS

SERGENT, Ed. Le Professeur Félix Mesnil. Zoologiste et Chef d'Ecole en Médecine coloniale. [**Professor Felix Mesnil, Zoologist and Chief of the Colonial School of Medicine.**] Reprinted from *Rev. de la Méditerranée.* 1948, v. 5, 24 pp.

DUBOIS, A. & DUREN, A. Soixante ans d'organisation médicale au Congo Belge. [**Sixty Years of Medical Organization in the Belgian Congo.**] *Liber Jubilaris J. Rodhain* (*Soc. Belge Méd. Trop., Brussels*). 1947, Dec., 1–36. [19 refs.]

This contribution to the *Liber Jubilaris J. Rodhain* contains an account of the development of the medical services of the Belgian Congo, with which, from 1903 to 1925, Rodhain was so closely associated ; he was the head of that service for five years. The service has grown from small beginnings, and as a result of special needs it has developed in various directions. For instance, the heavy incidence of sleeping sickness led to the development of a special section, which in turn has been expanded into the *Service d'Assistance Médicale Indigène* and finally into the Foréami service.

Training in medicine is given on a large scale to African auxiliaries and to the various subordinate grades, and schools for these purposes exist in nine cities. The government assumes responsibility for the health of the community, but encourages private initiative, for instance the Red Cross and university foundations, religious missions and the medical services of the big industries. In 1944 there were 176 physicians in government and Foréami service, 127 in other organizations, 15 private practitioners, and large numbers of *infirmières* and *agents sanitaires* [whose status is not here defined].

Scientific research in the Congo has a distinguished history, and there are now laboratories at 5 government stations and at various mines and Red Cross institutions. Scientific missions have played a great part in medical development, and continue to do so.

Of the important diseases, malaria is mentioned first. For trypanosomiasis the index of infection has fallen from 1·1 in 1927–29 to 0·23 in 1946 ($3\frac{1}{2}$ million examined in 1946). Schistosomiasis (mostly intestinal) is fairly common in the south and east, where *Planorbis adowensis* and *P. salinarum* are the snails. Vesical schistosomiasis does exist, however, and *Physopsis africana* is the host. The dysenteries, relapsing fever, leprosy (58,830 cases known), venereal diseases, cerebrospinal fever, yaws (quarter of a million treated each month ; permanently affecting 2–3 per cent. of the population), tuberculosis, plague, yellow fever, smallpox and murine typhus, are all important. Some of them are rather potential than actual sources of widespread danger, but all need, and receive, considerable attention.

The article is an interesting conspectus of the present situation.

Charles Wilcocks

SFORZA, M. Relazione Triennale (1945–1947) sull'attività del Laboratorio. **[The Work of the (Eritrea) Laboratory for the Period 1945–47.]** *Boll. Soc. Ital. di Med. e Igiene Trop.* (Sez. Eritrea). 1948, v. 8, Nos. 1/2, 31–53. [19 refs.]

The Laboratory of Hygiene and Prophylaxis of Eritrea has become also the Central Laboratory of Pathology and, with a staff comprising a director, an assistant, 6 technicians, an administrator, a registrar, and 4 laboratory boys (*uomini di servizio*) ; it deals with 100–120 specimens a day. For purposes of this report the work has been divided into five sections :

(1) *Biochemical*, dealing with 27,180 specimens, during the period, including examinations of urines, gastric contents, cerebrospinal fluids, blood samples and suchlike, not easily separated from

(2) *General microscopical and parasitological.* Search for intestinal protozoal and helminthic infestations, differential blood counts and blood parasites, malaria plasmodia and spirochaetes.

(3) *Serological*, including 36,520 Wassermann reactions, 5,056 Weil-Felix tests and preparation of antisera for precipitin reactions, blood grouping, etc. In an outbreak of typhus in Asmara in 1946–47, *Proteus OX19*, OX_2 and *OXK* were used. Reactions to the first-named were much the most numerous. Of 100 "nationals" [presumably Italians] 44 so reacted in a dilution of 1 : 1280 ; 5 to *Proteus* OX_2, while of 1,000 indigens the respective figures were 32·3 and 8·1 per cent.

(4) *Histological* and (5) *Bacteriological.*

An anti-rabies dispensary has been joined to the laboratory, where the vaccine is prepared and treatment given. The author states that undulant fever due to *Br. melitensis* and *paramelitensis* is a disease of the towns ; *Br. abortus* infection, he avers, does not occur. Bacillary dysentery is, apparently uncommon ; during the three years, 350 samples of faeces have been cultivated and the Shiga-Kruse organism has been isolated on 6 occasions, a Flexner organism 4 times and a Saigon strain once. Amoebic dysentery is more common, but not above "15–20 per cent." [the number examined is not, however, stated] and has become more widespread during and after the war years.

H. Harold Scott

SOUTH PACIFIC BOARD OF HEALTH. **Minutes of the Meeting held at Suva, Fiji, on the 25th, 28th and 31st October, 1946** [BUCHANAN, J. C. R., Chairman]. 6 pp. Fiji. Govt. Press.

At the inaugural meeting of the South Pacific Board of Health many subjects relating to that area were discussed. The Chairman, Dr. J. C. R. Buchanan, who holds the dual office of Inspector General, South Pacific Health Service and Director of Medical Services, Fiji, outlined the problems connected with health administration in the different islands and made it clear that the need was for integration, which would include a domestic interchange of epidemiological information.

The meeting discussed questions relating to establishment, research, diet and nutrition, epidemiology and training of staff. It is evident that the Board were fully alive to the nature of the problems facing them and of the need to take whatever steps to deal with them that might be available, in cooperation with neighbouring territories, large and small.

The establishment expenditure of the Service headquarters, and the estimates for 1945–46 are shown as appendices to the minutes.

H. J. O'D. Burke-Gaffney

NEDERL. TIJDSCHR. V. GENEESK. 1948, July 17, v. 92 (iii), No. 29, 2193–5. De gezondheidsdienst der residentie Zuid-Celebes. **[The Public Health Services of the South Celebes Residency.]**

South Celebes, the large island to the east of Java, has a homogeneous population of Malays, 4 million inhabitants, with a density varying from 2 to 200 per square kilometre. They are agriculturalists. Its capital, Makassar, headquarters of the public health service, has a population of 180,000, with one physician for 7,000 inhabitants.

An interesting account is here given of the principal diseases of the territory. One might have expected a reference to the Celebes vibrio, an even stronger competitor because of its cholera, not dysentery, syndrome, for equality status with the so-called " true " cholera vibrio than the El Tor variety. Cholera is not mentioned among the diseases of the island. Malaria is the most important sickness, with a heavy mortality toll among infants and young children. In some districts 50 to 90 per cent. of the school children have large spleens, while some 300,000 out of 850,000 inhabitants of endemic areas suffer from chronic malaria. Malaria is, however, of small importance in the town of Makassar. Yaws is once again receiving the attention of the physician. Each patient should receive 3 salvarsan injections and every physician gives monthly some 1,000 injections, in some cases up to 4,000. There is serious shortage of salvarsan. Other diseases mentioned are: avitaminoses such as beriberi, hookworm, endemic goitre, leprosy, tuberculosis, rabies and mental diseases. Filariasis and trachoma are not much in evidence.

Mortality and birth statistics are not yet forthcoming. Venereal diseases are not troublesome in rural areas, but are increasing in Makassar.

W. F. Harvey

BRITISH GUIANA, MOSQUITO CONTROL SERVICE. MEDICAL DEPARTMENT. **Annual Report for the Year ended 31st December 1947** [EDDEY, L. G., Deputy Director of Medical Services & Acting Chief Officer]. 7 mimeographed pp.

The Yellow Fever Service and the Malaria Research Service in British Guiana have now been amalgamated into the Mosquito Control Service, but the two sections, for *Aëdes* control and for DDT spray, are kept separate. The former comprises 82 and the latter 78 persons, and the office a staff of 4.

No *Aëdes* were found, during the year's searches, in Georgetown, Demerara River Estuary, Bartica etc., Mackenzie-Wismar, New Amsterdam, Berbice, or in trains. In these areas routine measures are taken against breeding, and 5 per cent. DDT in kerosene is extensively used as a spray at an estimated dosage of 150 mgm. DDT per square foot. All trains were re-sprayed during July and August.

Precautions against introduction of insects by air are taken by the authorities of the U.S. Air Base, and local British Guiana Airways aircraft are disinsectized by the company. Inter-colonial schooners and government ships are sprayed with DDT from time to time, with good results, and large ocean-going vessels, which are treated with DDT, are no longer sources of reinfestation.

Yellow fever immunity surveys were continued, 220 sera being examined at the Rockefeller Foundation Laboratory, Bogotá, Colombia ; of these 34·1 per cent. were positive for protective bodies. The specimens were mostly taken from people in the interior, and positive results were obtained in children ; these findings indicate that jungle yellow fever still occurs to a considerable extent in the Aboriginal Indians.

No viscerotomy specimens were received during the year, and no cases are reported from hospitals. Vaccination is carried out as required in Georgetown.

Total general expenditure was 182,792 B.W.I. dollars. *Charles Wilcocks*

IRONS, E. E. **Report of the Medical Mission to Puerto Rico and to the Virgin Islands.** *J. Amer. Med. Ass.* 1948, Apr. 10, v. 136, No. 15, 979–84.

The author was a member of a medical mission of 8 eminent medical men and one woman (Director of a school of nursing in Chicago) who were invited by the U.S. Secretary of the Interior to report on medical conditions in Porto Rico and the Virgin Islands, early in 1948. He reports his general impressions in this article, which has considerable interest for medical administrators of tropical countries.

The greatest single factor in the health of the people of Porto Rico is that of nutrition ; the total food supply, locally produced and imported, is not enough for the population of over 2,000,000, which is increasing by 65,000 each year. Some improvement may come from development in the use of fruits like mangoes and guavas, at present little used, and of fish, but that improvement cannot be great. It has been suggested that emigration would keep the population within reasonable limits, but this would need to involve over 50,000 each year. Increase in industrialization on present lines cannot cope with more than part of the problem. The net reproduction index of Porto Rico is 1·7, the highest in the world, and the 27 birth control clinics have so far had no demonstrable influence on the birth rate.

There are about 800 physicians, 200 of whom live in or round the capital, San Juan. The country districts are poorly supplied. Many of the doctors of municipal and district hospitals receive 300 to 450 dollars a month, and some give good service in return, but according to the author, many more give poor service. There are 65 type A rural health units and 21 " type B, or purely public health, units ". These serve the country districts, but they are not described ; the service at some is said to be very poor.

There are 5 district hospitals and 2 others are planned ; most of these are good and have recently improved under the guidance of Dr. J. A. PONS, the commissioner of health. There are municipal hospitals in several towns, some good, some not. " Apparently the difficulty is largely due to the political domination of hospital operation and the employment of physicians who have poor ideals or no ideals at all ". It would be wise to transfer these hospitals to the central government. Two hospitals for tuberculosis (and another projected), one for the insane, and one leprosy colony are also functioning, and there are several large private hospitals and clinics, which do excellent work.

For medical education, students go to the United States, and 160 are now there. If this process can be continued, the demand for doctors will eventually be met. In addition there is the group of " practicantes ", many of whom have been male nurses but who have expanded their activities and speak of themselves as minor surgeons. Their status was made legal in 1945, but " many of their performances are regarded as injurious to the persons on whom they work ". For post-graduate medical study the School of Tropical Medicine (which is conducted jointly by the government, the University of Porto Rico and the Columbia University) is, in the author's opinion, the greatest single factor in improving educational standards in medicine. It offers training in public health, and it operates a dispensary with 20,000 patients a year.

In the Virgin Islands the total population is about 30,000. Agricultural possibilities are slight, and the economic future may depend on tourists. Government care has been the rule for many years, in the provision of free

milk and free prescriptions, and "it is obviously difficult to administer free care and free food and at the same time to maintain any sense of responsibility in the individual". At St. Thomas (population 16,000–18,000) there are 3 physicians and a hospital with 89 beds, in which the patients are well treated. There are two hospitals and an institution for the aged at St. Croix. The medical services need to be expanded, and a fund is available for the purpose.

Charles Wilcocks

DE AZEVEDO, J. F. Relatório sobre as actividades do Instituto de Medicina Tropical em 1946. [**The Work of the Tropical Medicine Institute in 1946.**] *An. Inst. Med. Trop.* Lisbon. 1947, Dec., v. 4, 811–53.

DE AZEVEDO, J. F. Relatório de uma viagem de estudo aos Institutos Pasteur de Marrocos (Casablanca), Argélia (Argel) e Túnis e a alguns serviços médicos do Egipto. [**Account of a Study Trip to Pasteur Institutes in North Africa and of some of the Medical Services in Egypt.**] *An. Inst. Med. Trop.* Lisbon. 1947, Dec., v. 4, 501–66, 65 figs. (2 maps).

CAMBOURNAC, F. J. C. Relatório de uma viagem de estudo à América do Norte e a alguns paises das Américas Central e do Sul. [**Account of a Study Trip to North America and Parts of Central and South America.**] *An. Inst. Med. Trop.* Lisbon. 1947, Dec., v. 4, 567–655, 73 figs.

COMMONWEALTH OF AUSTRALIA. SERVICE PUBLICATION (DIVISION OF VETERINARY HYGIENE). 1947. No. 2. 41 pp. **Host Check List of Helminth and Arthropod Parasites present in Domesticated Animals in Australia. With Notes on their Presence in the several States and Lists of Parasites which have not become established, Doubtful Records, etc.**

BOOK REVIEWS

GILROY, A. B. [O.B.E., M.B., B.S. (Melb.), D.T.M. & H. (Eng.), Principal, India Branch of Ross Institute, etc.]. **Malaria Control by Coastal Swamp Drainage in West Africa.** pp. viii +97, 10 figs., 3 maps & 22 pls. 1948. Published by the Ross Institute of Tropical Hygiene, London School of Hygiene and Tropical Medicine.

The necessity for securing close collaboration between health officers and engineers in the planning and construction of engineering projects in malarious countries is now generally recognized. In India it is now an established principle that no large engineering project shall be planned without consultation with a malariologist, and that a specific sum shall be provided in the budget estimate for any antimalarial work that may be required. In some countries, notably in the U.S.A., many engineers have specialized in antimalarial drainage, and more than one has become an acknowledged authority on mosquito bionomics. In others, as in Malaya, health officers have acquired considerable practical knowledge of engineering methods, and have undertaken drainage work on an extensive scale. The mastery of swamp drainage technique displayed by Dr. Gilroy in the book under review places him in the latter category.

The author, who commanded a Malaria Field Laboratory in West Africa during the second world war, and was subsequently Malariologist to the Government of Nigeria, was in charge of a scheme designed primarily for the eradication of potential breeding places of *Anopheles melas*, a malaria vector of major importance in the neighbourhood of Lagos. There are three swamp

zones in this region, the first of which is completely submerged by the diurnal neap tides, the second for a few days monthly by the spring tides, and the third only twice each year by the high equinoctial springs. The second zone, in which occur extensive groves of the white mangrove, *Avicennia nitida*, is characterized by large-scale breeding of *A. melas*, whilst the first and third are comparatively innocuous. Control of breeding by means of larvicides had proved ineffective, and recourse was therefore had to swamp drainage on an extensive scale.

The scheme was initiated in 1942, for the control of malaria among Service, and particularly among R.A.F., personnel. It was continued after 1944 as a government undertaking, financed from Colonial Development and Welfare funds. In all, more than six square miles of swamps lying within the urban district of Lagos have been successfully drained.

By a fortunate chance, the R.A.F. personnel detailed for the project at the commencement of operations included a Norfolk hedger and ditcher, a borough council navvy and a landscape gardener's mate, all men accustomed to digging and hard manual labour in general. To each of these was assigned a squad of 50 Africans for training, and thus a nucleus of skilled diggers was created round which the main body of the labour force was subsequently built up. There can be no doubt that the success of the scheme was largely due to the high quality of the supervisory staff, and to the sustained enthusiasm which Dr. Gilroy was able to maintain among all those engaged in the operations.

Since no satisfactory attempt at drain excavation can be made in a swamp subject to flooding until the tides are excluded, the first stage in swamp drainage is the construction of a protective bund. Contour drains are dug, following the margin between the swamp and the higher land behind it, and these are connected to the main drains so as to conduct the water collecting in them by as short a route as possible to the lagoon. Subsidiary drains are constructed where these are found essential, but as in every good drainage scheme all drains are restricted to the absolute minimum necessary for the effective drying of the land.

Sluices, constructed with the aid of coffer dams, are placed in the bund at the outfall of each main drain. These are operated by hand, the possibility of using automatic sluices having been ruled out because of the very small head of water involved. Breeding of anopheline mosquitoes is very rare in well-maintained drains, as also in the numerous crabholes formed in the bunds. Fortunately, these latter have not proved a serious cause of damage to the banks.

The organization of swamp drainage in the Lagos area is based on the task system, which is preferred on the grounds that it entails a minimum of supervision, needs less attention to punctuality, allows of accurate estimation of quantities of work and is popular with the labourers, who know that the better they work the sooner they will be allowed to go home. Special attention is given to the training of foremen and the necessity for effective backing in the execution of their duties on the part of the European staff is emphasized.

The financial aspect of the project is treated in detail, the method of recording daily costs being of especial interest. By the system adopted, a balance is struck from day to day between available funds and amounts expended. This relation, viewed in the light of works progress, indicates whether or not the two are keeping pace. The cost of maintenance, where the aim is complete and continued eradication of anopheline breeding, averages about 15 per cent. of the original outlay. A progressive decrease in annual expenditure is expected after the consolidation of the earth work is complete.

The book comprises two main sections, the first giving a detailed account of the practice of swamp drainage, the second describing in comprehensive terms the organization of a swamp drainage scheme. Other sections deal with the

financial aspect of the project, the legal aspect of antimalarial operations and the maintenance of drained swamps. There are appendices reproducing the various forms used in the operation of the scheme, as also a summary of standing orders for maintenance workers and the provisions of a government ordinance relating to mosquito destruction. There are also a number of excellent photographs, maps and diagrams, among which a series of sketches by Mrs. Gilroy deserves special mention.

The text is written with clarity and vigour, and contains a wealth of information relating to the essential requirements on which depend the success or failure of an antimalarial drainage scheme. Every sentence contains matter of practical importance to the field worker. The title suggests that the subject matter is limited to coastal swamp drainage, but the book will be of service to those engaged in antimalarial drainage in any type of terrain, for the basic principles on which the success of all such schemes depends are essentially similar. Moreover, though written primarily for health officers, it will be helpful also to others connected with antimalarial schemes, administrators and field workers alike. Health authorities in malarious countries will be well advised to order copies of this book for distribution to all members of their staff who are likely to be called upon to plan or supervise antimalaria drainage works. It might with advantage be circulated also to hydraulic engineers operating in such regions, who do not always appreciate the essential differences between swamp drainage as a purely engineering problem and as an *Anopheles* eradication measure.

G. Covell

SANDOSHAM, A. A. **Malaria in Malai. A Handbook for Anti-Malaria Students.** With a Foreword by T. SATO. pp. xv+288, 22 figs. & 8 pls. (5 coloured). [Bibliography.] Reprinted with corrections 1945. Syonan [Singapore], Syonan Tokubetu-Si.

No claims to originality are made for the subject matter contained in this book. It is a compilation from many sources, put together in the form of lecture notes and then expanded into an elementary text book to suit the course of studies in malariology organized by the Health Department in Malaya.

The author divides his subject into seven sections: the first is mainly historical, but also contains general remarks on blood parasites and stains; the second section [part of which will have to be rewritten since the discoveries of SHORTT and GARNHAM] introduces the beginner to the malaria parasites, questions of immunity, climate, endemicity and epidemicity in Malaya. The anopheline mosquitoes of the country are dealt with in the third section. The fourth section is devoted to a good practical description of malaria and anopheline survey methods and the making of survey maps and reports. Section five deals with control and describes the usual well-tried ways of draining, oiling and so on, followed by notes on treatment and drug prophylaxis. Again, parts of this section need to be brought up to date. For example, the formulae for Dover's cream and Bamber oil are given, but dimethyl phthalate is not mentioned; the various formulations of DDT are omitted; and there is no reference to paludrine. A useful brief section on culicine mosquitoes comes next and the seventh section contains appendices on instructions in microscopy and the preparation of thin and thick blood films and staining. Aids to the identification of malaria parasites describe side by side the appearances of the different species in thin and thick film preparations, and aids to the identification of seventeen out of some forty species of Malayan anopheline species include illustrated descriptions of the main distinguishing characters.

There is a full index, but no attempt has been made to give a full list of references to works which have been consulted or from which data have been

extracted. Twenty publications are listed, none of which is later than 1940. The coloured plates illustrating malaria parasites seem to be reproductions of coloured pencil drawings.

[The book was first published in 1944 and reprinted in 1945. The author has undoubtedly performed a useful service in gathering together into one volume the kind of information necessary to and, indeed, often demanded by students of malaria and mosquito control. The absence of references to the more recent advances in knowledge, made during the war years and since the volume first appeared, is unfortunate but understandable, and it is to be hoped that settled conditions will soon permit the new knowledge to be incorporated in the next reprinting.] *H. S. Leeson*

ADOLPH, E. F. and Associates [Dept. of Physiology, University of Rochester]. **Physiology of Man in the Desert.** pp. xiii+357, 184 figs. 1947. New York & London: Interscience Publishers, Inc. [39*s*.]

During the war years much research on the responses of man to his thermal environment was sponsored by the United States Office of Scientific Research and Development, and prominent among the scientists engaged on this work were the authors of this book. Adolph's work on water balance is well known, and in their wartime studies he and his colleagues were largely concerned with the water and heat metabolism of man in the desert.

The book is a cooperative effort of the members of the Rochester Desert Unit. It deals with body heat exchanges, sweat formation and water turnover in a general way, and then turns to specific problems of life in the desert. Rates of sweating, urinary excretion, fluid intake, water requirements and water shortage are discussed. Then come chapters dealing with various aspects of dehydration, on survival without drinking water in the desert, and on the water losses of men on life rafts. In a chapter comparing tropical with desert conditions there is a useful discussion of the physiological assessment of environmental stress. For comparing the stresses imposed by desert and tropical environments, the authors use as their index the rate at which the body gains heat from the environment.

The penultimate chapter, by Adolph, includes a discussion of the factors which render and keep a man "desertworthy". There is a final chapter of summary and conclusions, and the last few pages of this give practical conclusions of great value to those responsible for men in the desert.

This book is a highly important contribution to environmental physiology. It contains a wealth of information sometimes in tabular form, sometimes in clear diagrams, and sometimes in the form of beautifully produced maps.

Although it appears as one of a series of monographs on the physiological sciences it will appeal to many who are not physiologists. It is clearly written and extremely interesting, and it is well produced. *Thomas Bedford*

PASSMORE, R. [M.A., D.M.Oxford, Captain, Indian Medical Service; Nutrition Research Laboratories, Indian Research Fund Association, Coonoor, S. India]. **Nutritional Diseases in India described for Students and Practitioners.** pp. viii+126+iv, 15 figs. on 13 pls. & 2 maps. 1948. Calcutta: U.N. Dhur & Sons Ltd. [Rs. 10.]

The book is written primarily for the medical student and practitioner in India. The author feels that hitherto these categories have fallen between two stools—the detailed book on nutrition written for the research worker and the popular book on nutrition written for the non-medical public.

The first chapter is appropriately on the causes of sickness and death in India and their relation to diet. The opening paragraph could not have been better chosen for it consists of Sir Alexander Russell's oft-quoted words on the over-riding importance of the recognition of the dietary defects of the population of India whatever disease is being specifically considered from the preventive aspect. The author then proceeds to consider the causes of death in India and to point out the part played by defective nutrition in each case ; he has usually backed his argument by statistics from the Public Health Commissioners' reports or from those of provincial directors of public health. The diseases discussed include malaria and " fever ", dysentery and diarrhoea, respiratory diseases, and leprosy ; infantile and maternal mortality are also included. Most of the arguments are well-known to the reviewer, but this will probably not be the case with the general reader who may not be quite so familiar with the subject and the author will certainly make his point. Somewhat surprisingly most of his statistical data are at least 10 years old.

The chapter ends on the note on which it began ; the author points out that the nutrition problem can only be tackled by revolutionary changes in agriculture and in the social, political and religious life of the community, and that, although it is not the doctor's business to bring these about, it is his business to point out how necessary they are.

The second chapter is on malnutrition, and generally speaking it is a very satisfactory one. The author has described the stigmata of malnutrition without necessarily specifying which particular food deficiency is responsible for each defect. This is a healthy modern tendency in nutritional studies ; it has been necessitated to some extent by the obviously mixed aetiology of most clinical manifestations of malnutrition, and by the many mistakes that have been made in the past through unjustifiable dogmatism. The chapter concludes with a discussion on treatment of malnutrition. Interpolated in the middle of this chapter, under a section headed " The Blood and Urine ", are a few remarks in very small print on sprue and ariboflavinosis. The impression conveyed is that this was an afterthought, late in the production of the book when the author suddenly discovered that he had not mentioned these two words, neither of which as words he appears to like.

His paragraph on sprue opens and concludes thus :—

" Sprue is a condition very similar to the picture of malnutrition already described . . . nutritional diarrhoea is a sound descriptive diagnosis, preferable in most instances to ' sprue ', a Dutch word apparently meaning an inflammation of the tongue ". It is felt that the after-thought, if it was one, was unfortunate and that it would have been better to have ignored the disease, which as it is seen in the European does not, in the reviewer's opinion, play any part in the nutrition problem of the native of India.

In Chapter 3 is given a good description of certain specific deficiency diseases, beriberi, pellagra, scurvy and rickets and osteomalacia.

The next chapter is on anaemia in relation to nutrition. It is not one of the better chapters of the book ; the author does not seem very familiar with the subject and did not write a very orderly chapter, although he started appropriately with physiological considerations and a reference to Whipple's work on blood formation and diet. His short excursion into haematological methods was unfortunate ; for no very good reason he chose to describe the method of calculation of the mean corpuscular values, MCV and MCHC, and got the first one wrong (possibly a misprint, but it is repeated).

The next two chapters are again sound ones ; they are on " Diseases probably due to food poisons " and " Miscellaneous Diseases in which the Errors in Diet *may* be a Contributory Factor ", respectively. However, the publishers evidently did not approve of the author's doubts and have called them

"Diseases due to Food Poisons" and "Diseases caused by Errors in Diet" on the page headings. The former include lathyrism and epidemic dropsy and the latter tropical ulcer, goitre, peptic ulcer, diabetes, dental disease, cirrhosis of the liver, and urinary stone. The author, however, is unequivocal in his opinion that diet has little to do with stone formation.

The book concludes with a number of useful appendices, food analyses, diet tables, etc.

It is a book that will serve its purpose well. It is pleasing to handle and read and the price is moderate. The illustrations are mostly good and relevant, but it would have been better if they could have been distributed into their appropriate places in the book instead of being concentrated at the beginning. Finally, it is singularly free from misprints. However, for the sentence "The normal stimulus of thirst appears to be in obeisance" the reviewer, who has also published books in India, extends his sympathy to the author; in the words of John Bradford, "But for the Grace of God there goes . . . . . ."

L. E. Napier

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ALPHABETICAL LIST OF AUTHORS OR SOURCES

Abbott, P. H., 1037.
Adolph, E. F. & Associates, 1046.
Aguirre Pequeño, E. & Gonzalez, R. E., 1030.
Alleman, R. J. & Stollerman, G. H., (1026).
d'Almeida, J., (1032).
Altmann, A., 1025.
Alving, A. S., Craige, B., Jr., Jones, R., Jr., Whorton, C. M., Pullman, T. N. & Eichelberger, L., 953.
——, ——, Pullman, T. N., Whorton, C. M., Jones, R., Jr. & Eichelberger, L., 951.
——, Eichelberger, L., Craige, B., Jr., Jones, R., Jr., Whorton, C. M. & Pullman, T. N., 956.
——, Pullman, T. N., Craige, B., Jr., Jones, R., Jr., Whorton, C. M. & Eichelberger, L., 954.
Ansari, M. Y., 973.
Ansell, I., 946.
Aru, L., 970.
Atkins, W. R. G., 1019.
de Azevedo, J. F., (1043) *bis*.
——, Cambournac, F. J. C. & Pinto, M. R., 966.
——, Teixeira, A. W. G. & Coito, A. de M. F., 985.

Baligh, A., 999.
Barnett, S. A., 998.
Basham, E. H. & Haeger, J. S., (969).
Bechelli, L. M., 1010, 1014.
Belvere, L., 947.
Berliner, R. W., Earle, D. P., Jr., Taggart, J. V., Welch, W. J., Zubrod, C. G., Knowlton, P., Atchley, J. A. & Shannon, J. A., 961.
——, ——, ——, Zubrod, C. G., Welch, W. J., Conan, N. J., Bauman, E., Scudder, S. T. & Shannon, J. A., 960.
——, Kennedy, T. J., Jr. & Bigelow, F. S., 964.
Blake, W. D., 965.
Boquet, P., 1027.
Bourgain, M. & Bazil, A., 1031.
Braga, R. V., 1007.
Brisou, J. & Autheman, R., 987.
British Guiana, 976, 1041.
British Med. J., 983.
Brosius, O. T., Thomas, E. E. & Brosius, B., 1023.
Buchanan, J. C. R., 1040.

Callot, J., 1036.
—— & Vendrely, R., 990.
Cambournac, F. J. C., (1043).
Causey, O. R., Laemmert, H. W., Jr. & Hayes, G. S., 992.
Chabaud, A. G., 994.
Chalgren, W. S. & Baker, A. B., 1034.
Chaussinand, R., 1008, (1008), 1009, 1012.
Chen, K. C., 1022.
Chorine, V. & Crougue, O., (1014).
Clarke, D. H. & Fox, J. P., 986.
Coito, A. de M., 1019.
Commonwealth of Australia, (1043).
Contreras, F. & Jaqueti, G., 1008.
Coutinho, J. de O., (969).
Craige, B., Jr., Eichelberger, L., Jones, R., Jr., Alving, A. S., Pullman, T. N. & Whorton, C. M., 953.

Davey, T. F., 1012.
DeLamater, E. D., 1030.
Dick, M. I. B., Harrison, I. T. & Farrer, K. T. H., (1027) *bis*.
Drill, V. A. & Loomis, T. A., 1023.
Dubois, A. & Duren, A., 1039.
Dwork, K. G., 1005.

Earle, D. P., Jr., Berliner, R. W., Taggart, J. V., Zubrod, C. G., Welch, W. J., Bigelow, F. S., Kennedy, T. J., Jr. & Shannon, J. A., 963.
——, ——, ——, Welch, W. J., Zubrod, C. G., Wise, N. B., Chalmers, T. C., Greif, R. L. & Shannon, J. A., 957.
——, Bigelow, F. S., Zubrod, C. G. & Kane, C. A., 962.
——, Welch, W. J. & Shannon, J. A., 959.
Earle, K. V., 1029.
East Africa High Commission, 982.
Eddey, L. G., 1041.
Erhardt, A. E., (1020), 1023.
Eskey, C. R. & Hemphill, F. M., 990.

Fain, A. & Henrard, C., 967.
Fay, R. W., Cole, E. L. & Simmons, S. W., 1037.
Fernández, J. M. M. & Bergel, M., 1013.
——, Carboni, E. & Tomassino, P., 1012.
Ferro-Luzzi, G., 1017, 1024.
Fiol, H., Jonquieres, E. D. L., Brusco, C. M., Melamed, A. J. & Firpo, C. J., 1011.
Firlotte, W. R., 1010.
Fitzhugh, O. G., Nelson, A. A. & Holland, O. L., 978.
Flachs, A., 1026.
Frank, H. R. & May, K. H., 988.

Gaase, A., 987.
Gaud, J., Fauré & Solé, 1015.
Ghosh, N. N., Ghosh, H. & Ray, J. C., 1002.
Giglioli, G., 976.
Gilroy, A. B., 1043.
Gingrich, W. D., 980.
Giraud, P., Bernard, R. & Bergier, P., 984.
Glauner, W., 1006.
Gohar, M. A. & Isa, A. A., 1000.

v. Haller, E., 970.
Hare, K., 1032.
Hassan, A., 998.
Hopkins, G. H. E., 995.
Hu, S. M. K., 1022.
Huang, C. H., Huang, C. Y., Chu, L. W. & Huang, T. F., 996.
Hullshoff, A. A., (1004).

In der Beeck, M., (998).
Innes, E. M., 1026.
Irons, E. E., 1042.

Jones, R., Jr., Craige, B., Jr., Alving, A. S., Whorton, C. M., Pullman, T. N. & Eichelberger, L., 951.
——, Pullman, T. N., Whorton, C. M., Craige, B., Jr., Alving, A. S. & Eichelberger, L., 955.

Kahlstorf, A., 972.
Kettle, D. S., 967.
Kopaczewski, W., (1010).

Lahiri, S. C., 1000.
Lampen, H., 970.
Lamy, L., Marchal, G. & Chevrier, A. M., 1006.
Lefrou, G., 981.
Lewis, D. J., 968.
Lichtenstein, E. P., (1037).
Lombard, F. F., (971).
Lübke, A., 988.
Luis Carri, E., (1006).

McCarthy, D. D. & Wilson, D. B., 993.
MacCarthy, E., (980).
McCoy, G. W., 1007.
Macdonald, A. B., 1014.
Macdonald, G., (975) *bis*.
MacFarlane, J. O. & Ruchman, I., 1035.
Macgraith, B. G., (973), (981).
Maier, J., 971.
Mara, L., (968).
de Meillon, B., 1037.
de Meira, M. T. V., Simões, T. S. & Noguseira, J. F. P., 1031.
Meyer, H. & Xavier de Oliveira, M., 983.
Meyer, K. F., Quan, S. F. & Larson, A., 997.
Montoya, J. A. & Osejo, P. P., 989.

Nash, T. A. M., 983.
Nederl. Tijdschr. v. Geneesk, 1041.
Negroni, P. & Radice, J. C., (1031).

Oey Oen Bie, 1020.
Olmos Castro, N., Arcuri, P. B. & Bonatti, A. A., 1010.

Palmer, L. G., 1004.
Passmore, R., 1046.
Peffly, R. L., Davidson, R. H. & Waters, H. A., (969).
Philip, C. B., 991.
Piaggio Blanco, R. A., Fernández Chapela, A. & Paseyro, P., (1023).
Pratt, H. D., 977.

Continued overleaf

ALPHABETICAL LIST OF AUTHORS OR SOURCES—*cont. from page 3.*

Pullman, T. N., Craige, B., Jr., Alving, A. S., Whorton, C. M., Jones, R., Jr. & Eichelberger, L., 955.
——, Eichelberger, L., Alving, A. S., Jones, R., Jr., Craige, B., Jr. & Whorton, C. M., 952.

Rabinowitz, E., Aschner, M. & Grossowicz, N., 986.
Rachmilewitz, M., Braun, K. & de Vries, A., 984.
Raffaelli, D., 1038.
Ramos, A. S. & Assoreira, M., (988).
Raper, A. B., 1017.
Remlinger, P. & Bailly, J., 945.
Rigdon, R. H., 978.
—— & Rostorfer, H. H., 979.
Roberts, F. H. S. & O'Sullivan, P. J., 968.
Robertson, J. D., 972.
Rodhain, J., 978.
Rosenfeld, M., Zubrod, C. G., Blake, W. D. & Shannon, J. A., 964.
Rotberg, A., 1013.
Rozeboom, L., (969).

Sandor, G., Girard, G. & Skrobisz, C., with Chevallier, A., 994.
——, Giroud, P. & Skrobisz, C., 986.
Sandosham, A. A., 1045.
Sarkar, N. K., 1028.
Schujman, S., 1010.
—— & Castañe Decoud, A., 1011.
Schwetz, J., 1015.
Scott, J. A., 1038.
Sellers, T. F., 946.
Sergent, Ed., (1039).
Sforza, M., 1040.
Shaffer, J. G., Ryden, F. W. & Frye, W. W., 1001.
Shannon, J. A., Earle, D. P., Jr., Berliner, R. W. & Taggart, J. V., 956.
Shepard, C. C. & Huebner, R. J., 992.
Siegert, R., 988.
Smith, R. E., Steele, J. M., Eakin, R. E. & Cowie, D. B., 985.
Snyder, B. L. & Rogers, G. K., 1031.
South Pacific Board of Health, 1040.
Stage, H. H., (1037).
Steiniger, F., 1008.
Stewart, G. T. & Jones, W. R., 1001.
——, O'Meara, P. J. & Kershaw, W. E., 1002.
Straus, B. & Gennis, J., 974.

Taggart, J. V., Earle, D. P., Jr., Berliner, R. W., Welch, W. J., Zubrod, C. G., Jailer, J. W., Kuhn, B. H., Norwood, J. & Shannon, J. A., 960.
——, ——, ——, Zubrod, C. G., Welch, W. J., Wise, N. B., Schroeder, E. F., London, I. M. & Shannon, J. A., 958.
Tisseuil, J., 980.
Toumanoff, C. & Hérivaux, A., 995.
Towne, C. E., (1023).
Trethewie, E. R. & Day, A. J., 1029.

Vachon, M., (1029).
Vincke, I. H. & Lips, M., 979.

Wahid, A. A., 998.
Walls, E. S., 972.
Warren, J. & Russ, S. B., 1035.
Wartman, W. B., 1020.
Waterhouse, D. F., 975.
—— & Atherton, D. O., 975.
Watson, J. M., Abdel Azim, M. & Halawani, A., 1018.
Weurman, C., (988).
Winckel, C. W. F., (971).
Winsser, J., Verlinde, J. D., van Thiel, P. H., Davel, J. & van der Elst, P., 1036.
World Health Organization, 948.
Wright, C. I. & Sabine, J. C., with Wright, A. H., 975.

Yoeli, M., 966.
Young, V. M. & Felsenfeld, O., 1005.

Zubrod, C. G., Kennedy, T. J. & Shannon, J. A., 962.

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